Clinical Health Journal

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The mediating effect of sleep disturbance on the association between hypertension and depression: a national data analysis

Teenage Blues: Predictors of depression among adolescents in Nigeria

Age-Related Hearing Loss

Understanding Sickle cell disease: Causes, symptoms, and treatment options

In
Hypertension, cardiovascular risk reduction

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BP: Blood pressure.
1. Cardiovasc J Afr. 2010 Feb; 21(1): 61–62.; 2. Drugs. 2006;66(1):51-83.;
3. Expert Opinion on Pharmacotherapy 2011;12(17):2719-2735

In
Dyslipidemia, CV event prevention

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- Greater LDL-C reduction (up to 55%) at lower dose, as compared to other statins[1]
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CVD: Cardiovascular disease | LDL-C: Low-density lipoprotein cholesterol
1. Clin Med Insights Cardiol. 2012; 6: 17–33.; 2. JAMA 2007 Mar 28;297(12):1344-53.;
3. Journal of the American College of Cardiology 2017;69(22).;
4. ACC/AHA CLINICAL PRACTICE GUIDELINE; Circulation 2019; 140(11): e596-e646.

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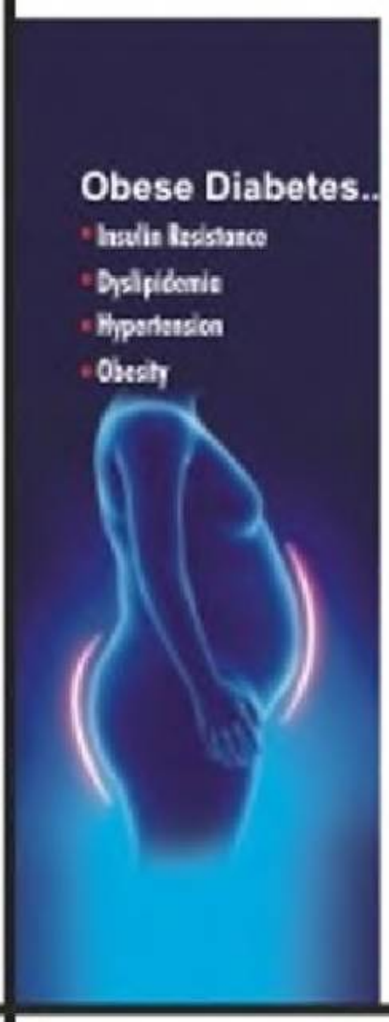

Obese Diabetes..

- Insulin Resistance
- Dyslipidemia
- Hypertension
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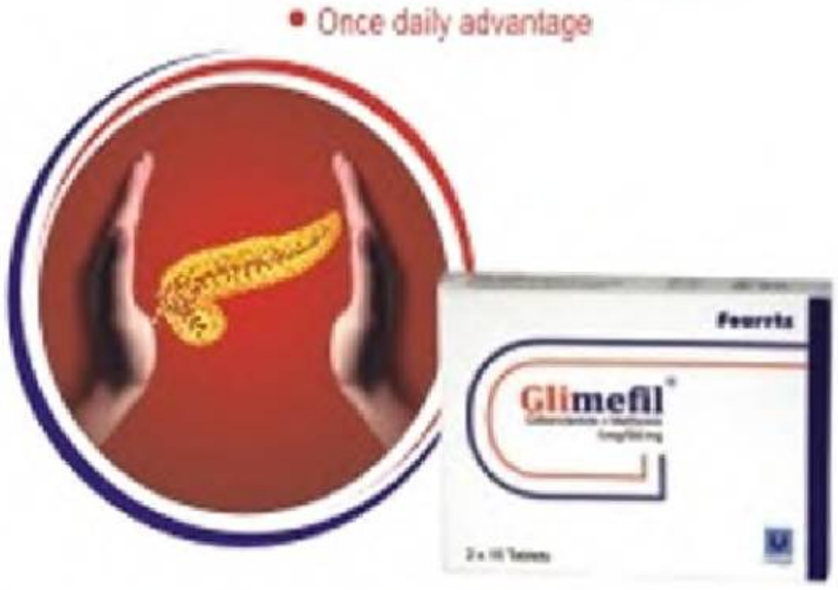

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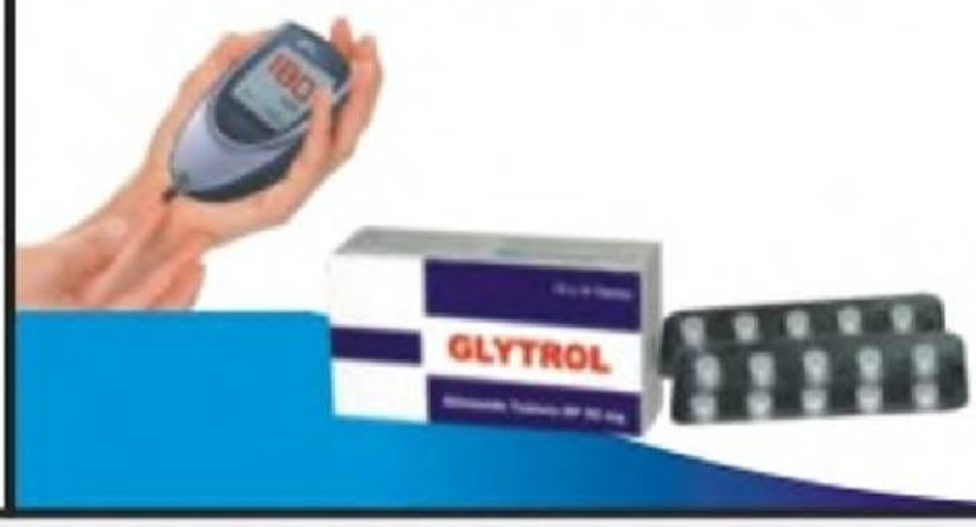

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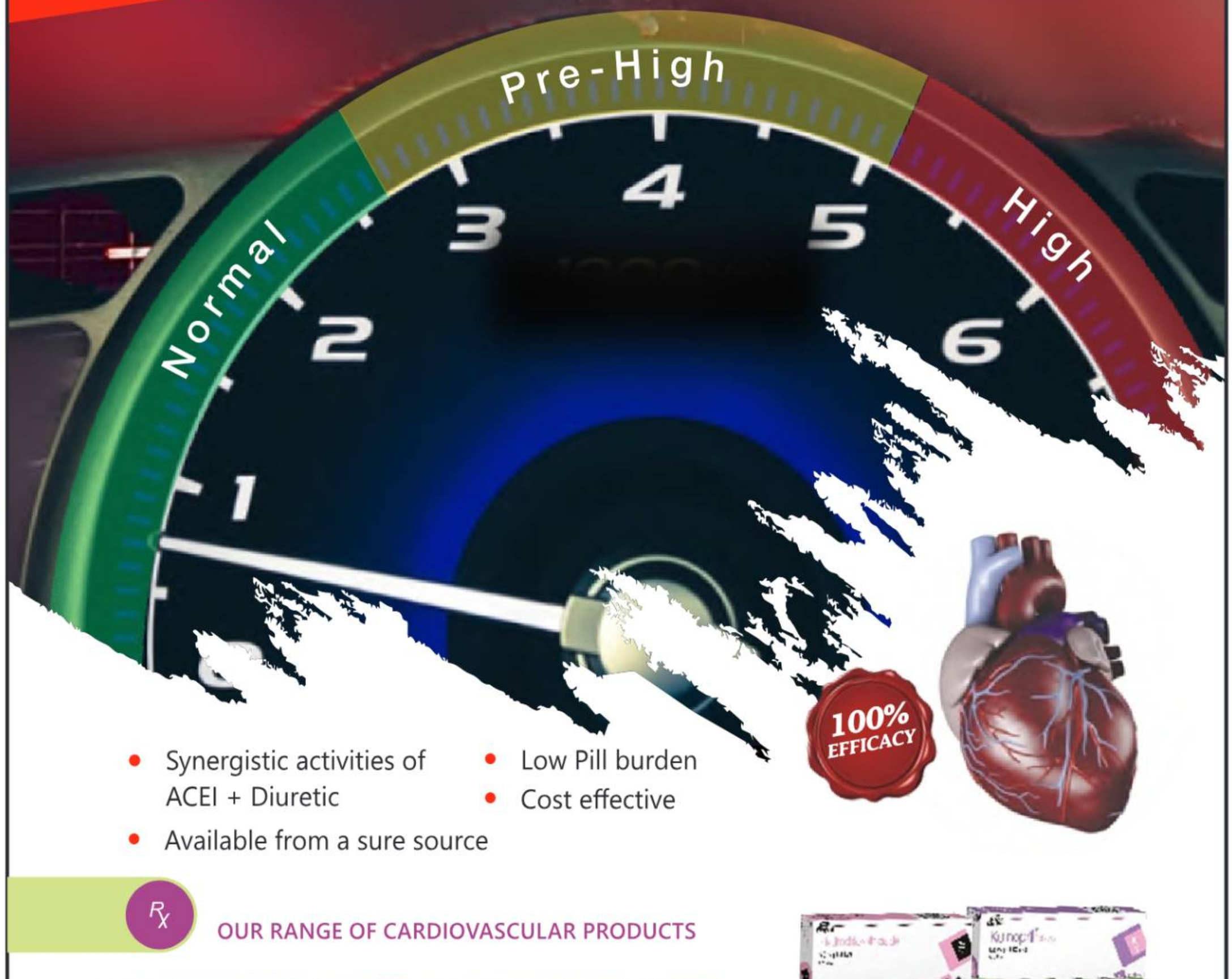

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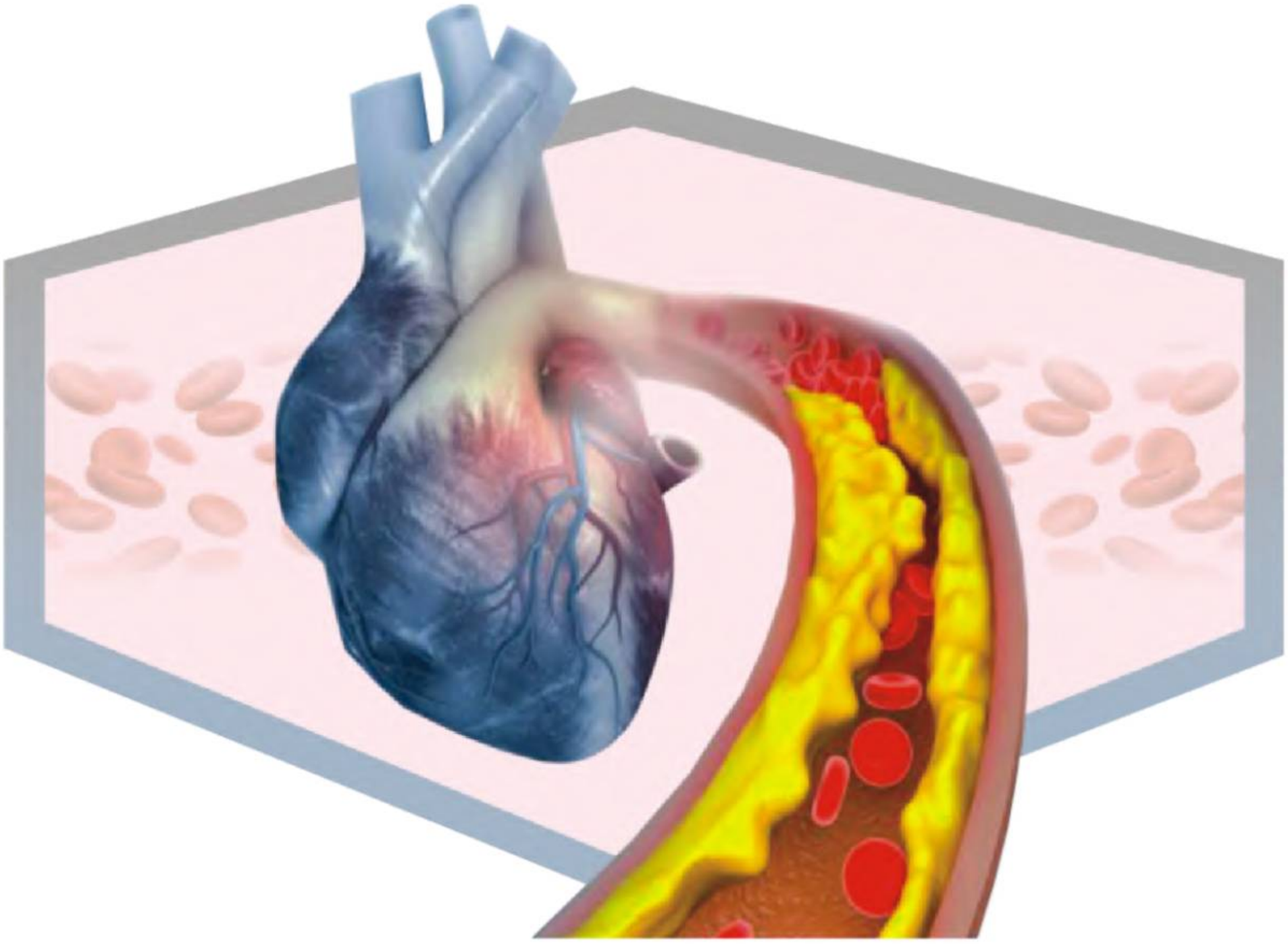

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The mediating effect of sleep disturbance on the association between hypertension and depression: a national data analysis

Kamaluddin Latief, Samuel Akyirem, Siriluk Sithichoksakulchai, Dieta Nurrika, Mokh. Sujarwadi & Faizul Hasan

Abstract

Background

Sleep disturbance is a common among people with hypertension. However, the mediating role of sleep disturbance in the association between hypertension and depression remains unclear. This study aims to investigate the mediating role of sleep disturbance in the association between hypertension and depression.

Materials and methods

This was cross-sectional study. The data were derived from the Indonesian Family Life Survey Fifth Wave (2014–2015). We include a total of 19,138 adults' participants with age range from 18 to 65 years old who completed response on the variable of hypertension, sleep disturbance, and depression. The mediating model analysis was processed using the PROCESS macro ins SPSS from Hayes model.

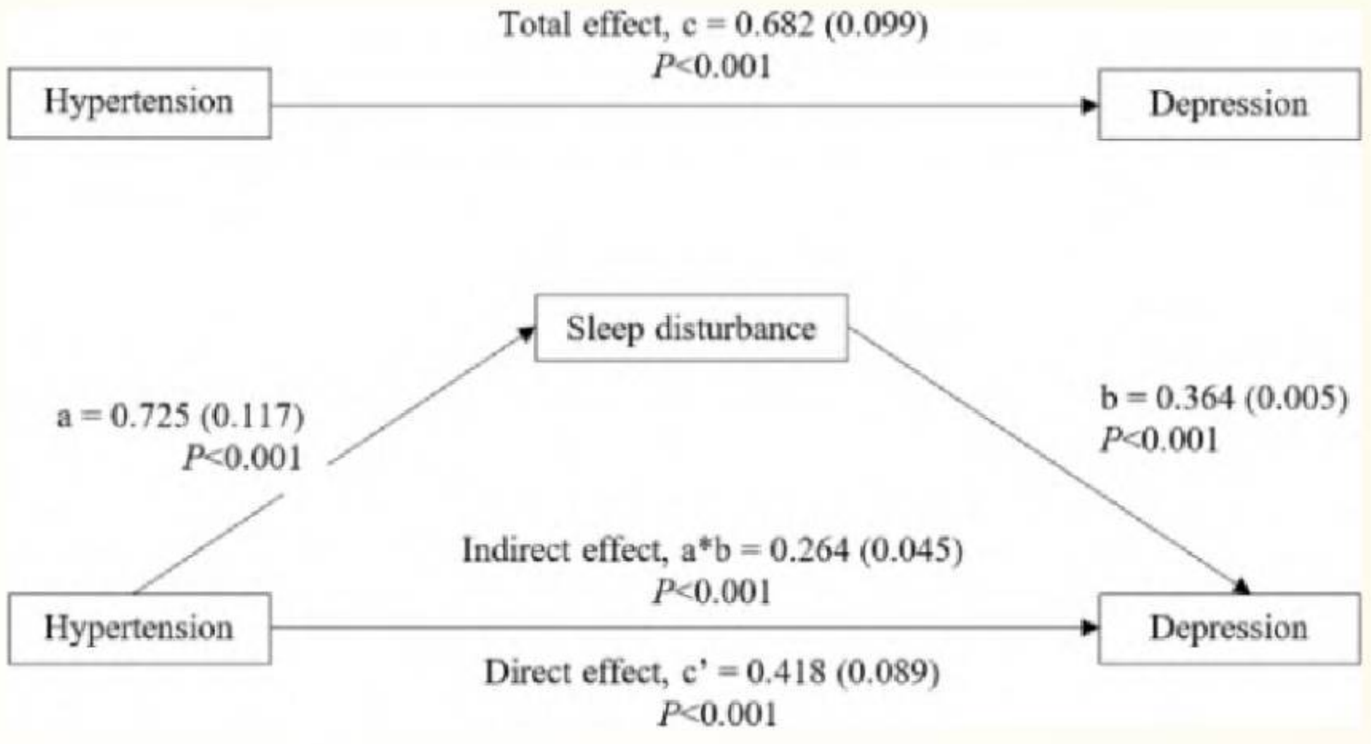
Results

Depression was reported by 22% of total respondents. The group with hypertension showed a substantially higher prevalence of depression than non-hypertension group (P < 0.001). Hypertension had a significant overall effect on depression (β = 0.682; 95%CI 0.489 to 0.875, P < 0.001). The direct effect of hypertension on depression was significant (β = 0.418; 95%CI 0.244 to 0.592, P < 0.001) and the indirect effect that mediated by sleep disturbance was also significant (β = 0.264, 95%CI 0.174 to 0.356, P < 0.001). It is worth noting that sleep disturbance partially mediated the association between hypertension and depression.

Conclusion

The findings of this study indicated that sleep disturbance contributed to the etiology of depression and hypertension in adult populations. Nurses should be involved in managing sleep disturbances, such as using behavioral therapy, as it may serve as both a treatment and primary prevention measure for depression and hypertension.

Graphical Abstract



Background

Hypertension is a common chronic condition with global prevalence ranging from 31 to 56% [1,2]. In Indonesia, about 8.4% of adults have been diagnosed with hypertension by a medical doctor [3]. Hypertension has been linked to elevated risk of cardiovascular comorbidities including stroke [4] and chronic kidney diseases [5,6]. Other evidence suggests that people with hypertension are more likely to experience depression [7,8].

Several studies have reported prevalence rates ranging from 22 to 32% [7,9]. Previous studies suggest a bidirectional association between hypertension and depression [9,10]. Depression may increase the risk

of hypertension by activating the body's stress responses and increasing autonomic nervous system activation [11]. On the other hand, hypertension may increase the risk for depression by causing cerebrovascular pathologies [12] and increasing the sense of hopelessness related to living with a chronic condition [13]. People who suffer from both depression and hypertension often report low quality of life [14]. In addition, they often experience sleep disturbances [15]. While, the underlying mechanism of the hypertension-depression relationship remain complex, sleep disturbance has been identified as a potential mediator [15].

Sleep disturbance has been linked to physical and mental health including cardiovascular disease and mood disorders [16]. People with sleep problem have high risk to develop hypertension [17] and depression [18]. However, there is a lack of study investigating the mediating role of sleep disturbance in the association between hypertension and depression. Hence, in this study we aim to investigate the mediating role of sleep disturbance in the association between hypertension and depression using nationally representative data from Indonesia.

Materials and methods

Data source and participants

The data was derived from Indonesian Family Life Survey (IFLS) fifth Wave (IFLS-5), which is a cross-sectional study, fielded in September 2014 to April 2015. The IFLS sample represents approximately 83% of the Indonesian population living in 13 of the country's 26 provinces, covering 16,204 house- holds and 50,148 individuals [19]. The IFLS has been conducted 5 times, in 1993, 1997, 2000, 2007, and 2014. The details of study design of the IFLS-5 have been previously described [19]. In this study, we include a total of 19,138 adults' participants with age range from 18 to 65 years old who have completed response on the variable of hypertension, sleep disturbance, and depression.

Ethical approval

The IFLS data are accessible to the general public. Institutional review boards at the University of Gajah Mada in Indonesia and the RAND Corporation in the United States have examined and approved the survey's methods with the ethical clearance No.s0064-06-01-CR01 [19]. Before data collection began, all participants provided their written, informed consent.

Measurements

Depression

Depression was measured using the short form Centres for Epidemiologic Studies Depression Scale (CES-D-10) [20]. CES-D-10 consist of 10 items rated on a 4-point Likert scale ranging from 0 (rarely or none of the time) to 3 (all of the time) with higher score indicating more depressive symptoms. A total score of 10 or higher is indicative of having depression. Previous study revealed that this scale has acceptable validity and reliability [19].

Hypertension

Previous studies using IFLS data indicate that hypertension, as measured by blood pressure, covers approximately 40% of participants [21,22], while hypertension using self-reported measurements covers around 80% of participants [21]. Therefore, in this study, hypertension was assessed using self-report, measured with the question, "Has a doctor, paramedic, or nurse ever told you that you had hypertension?".

Sleep disturbance

Sleep disturbance was measured using the combination of five items of Patient-Reported Outcomes Measurement Information System (PROMIS) sleep disturbance measure [23] and five items of PROMIS sleep impairment measure [24]. Previous study reported that the scale has good Cronbach's alpha of 0.82 [25]. Higher scores on the scales indicate more sleep disturbance with a cut-off point 11 or higher indicating of having sleep disturbance [25].

Lifestyle and comorbidity condition

Smoking status was measured and classified into three groups (never, quitters and current tobacco users) [19]. Physical activity was measured using the short version of International Physical Activity Questionnaire (IPAQ) for the last 7 days (IPAQ-S7S) [26]. It is divided into three level of low, moderate, and high intensity physical activity. Additionally, for the outpatient care were assessed using single item questionnaire [19]. For comorbidity conditions (diabetes mellitus, tuberculosis, asthma, lung condition, heart attack, liver disease, stroke, cancer, high cholesterol, kidney disease, stomach or other digestive disease, and psychiatric problem). It was measured using single item question such as 'Has a doctor/paramedic/nurse/midwife ever told you that you had...? to which participants answered "yes" or "no" [19].

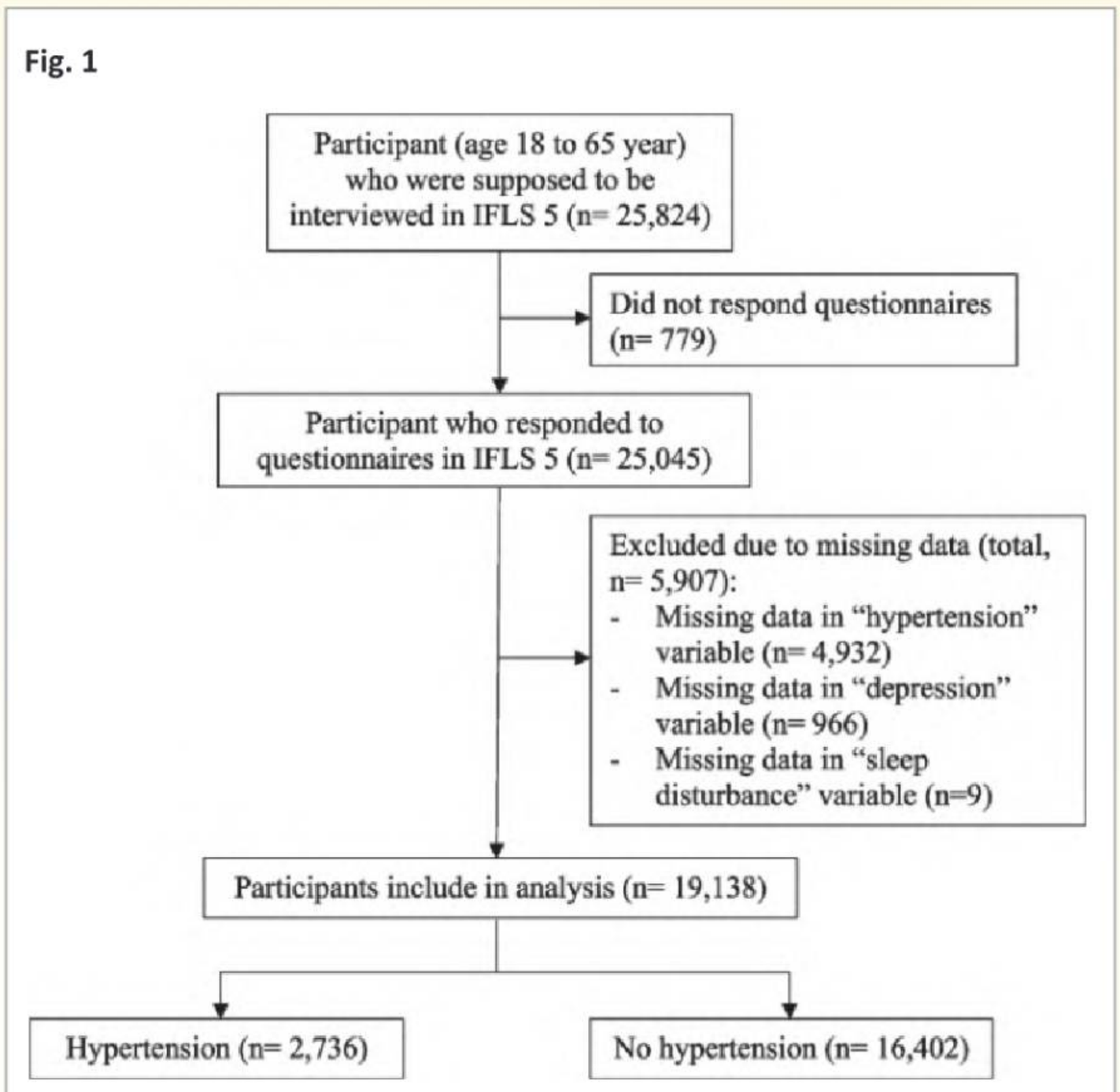
Demographic

In addition, demographic variable including age, gender, marital status, attending school, and education level were added in this study [19].

Statistical analyses

At the beginning, we used STATA software for all data processing. In the second stage, we used SPSS software version 29.0 to perform all statistical analyses (IBM, Armonk, NY, USA). A two-tailed of $P < 0.05$ was considered as a statistically significant level. To analyse the differences in the baseline characteristics between the 2 groups, we used the chi-squared or Fisher's exact test for categorical variables and independent t-tests for continuous variables. The correlation between main variable (hypertension, sleep disturbance, and depression) were measured using Pearson and Spearman correlation. Univariate and multivariate linear regression analyses were also performed. Finally, the mediating model analysis was processed using the PROCESS macro ins SPSS from Hayes model[27].

Fig. 1



Participant flow chart. *n* = number of participants

Result

Study characteristic

Figure 1 depicted the participants' flow diagram. In total, there were 25,824 adult participants were screened for eligibility. Of these, a total of 6,686 participants were excluded, with 779 not responding to questionnaires and 5,907 having missing data. This included missing data in the 'hypertension' variable (n = 4,932), 'depression' variable (n = 966), and 'sleep disturbance' variable (n = 9). Finally, a total of 19,138 participants were included in the main analysis. Hypertension was confirmed for 2,736 (14.3%) individuals.

Demographic comparisons between patients with hypertension (n = 2,736) and without hypertension (n = 16,402) were presented in Table 1. The prevalence of hypertension varies across age groups, with rates of 6.5% for the 18–34 age group, 13.1% for the 35–49 age group, and 25.9% for the 50–65 age group. Most of the participants were married (84%) and 96% of them have attended the school.

The comparison of lifestyle and comorbidity conditions were presented in Table 2. In total 37% of included participants were smoker. The hypertension group had higher sleep disturbance compared to the non-hypertension group. There is a significant difference between the two groups in terms of physical activity (vigorous and low activity levels) ($P < 0.001$ and $P = 0.001$, respectively). Other details of the variable can be seen in Table 2.

Depression

The depression was reported in 22% of the total sample. The group with hypertension had a significantly higher depression prevalence compared to the non-hypertension group (see Table 2, $P < 0.001$). Supplementary Table S1 presented the response of participants who endorse each of the depression questionnaires.

Association between the hypertension, sleep disturbance, and depression

Supplementary Table S2 shows the association between the hypertension, sleep disturbance, and depression. The hypertension variable had a significant positive correlation with depression ($r = 0.05$, $P < 0.001$). The hypertension variable also has a significant positive correlation with sleep disturbance ($r = 0.05$, $P < 0.001$). Similarly sleep disturbance variable also has a significant positive correlation with depression ($r = 0.44$, $P < 0.001$).

Table 1 Demographic comparison of participants

Variables	Total (n = 19,138)		Missing data		Hypertension (n = 2736)		No hypertension (n = 16,402)		p-value
	n	(%)	n	(%)	n	(%)	n	(%)	
Age									< 0.001
18–34 years	6410	(33.5)			418	(15.3)	5992	(36.5)	
35–49 years	7635	(39.9)			998	(36.5)	6637	(40.5)	
50–65 years	5093	(26.6)			1320	(48.2)	3773	(23)	
Gender			1	(0.0)					< 0.001
Female	10,469	(54.7)			1817	(66.4)	8652	(52.7)	
Male	8668	(45.3)			919	(33.6)	7749	(47.2)	
Marital status			4	(0.0)					< 0.001[a]
Single	1355	(7.1)			81	(3)	1274	(7.8)	
Married	16,058	(83.9)			2263	(82.7)	13,795	(84.1)	
Separated	102	(0.5)			12	(0.4)	90	(0.5)	
Divorced	487	(2.5)			68	(2.5)	419	(2.6)	
Windowed	1128	(5.9)			310	(11.3)	818	(5)	
Cohabitate	4	(0.0)			2	(0.1)	4	(0.0)	
Have you ever attended/ are you attending school?			2	(0.0)					< 0.001
Yes	18,365	(96)			2571	(94)	15,794	(96.3)	
No	771	(4)			165	(6)	606	(3.7)	
Education level			773	(4)					< 0.001
University level	1891	(9.9)			220	(8)	1671	(10.2)	
Below university level	17,247	(90.1)	2516	(92)	14,731	(89.8)			

Continuous variable was performed by using independent t-test,
Categorical variables were performed by using chi-square test or [a]Fisher's exact test

The bivariate and multiple linear regression results are displayed in Table 3. In the unadjusted model, all predictors show a significant positive association with the target variable. When hypertension and sleep disturbance are combined as predictors in Model 1, the association remains significantly positive. In Model 2, all predictors also exhibit a significant positive association with the outcome variables.

Mediating effect of sleep disturbance on the association between hypertension and depression

The simple mediating analysis indicated that sleep disturbance partially mediated the association between hypertension and depression. As shown in Fig. 2 and supplementary Table 3, hypertension was positively associated with sleep disturbance (a = 0.725), and sleep disturbance was positively associated with depression (b = 0. 364). Based on 5,000 bootstrap resamples, the bootstrap confidence interval for the indirect effect (ab = 0.264) was entirely above zero, ranging from 0.174 to 0.356. The total effect of hypertension on depression was significant (β = 0.682; 95% CI 0.489 to 0.875, $P < 0.001$), comprising a direct effect (β = 0.418; 95% CI 0.244 to 0.592, $P < 0.001$) and an indirect effect (β = 0.264; 95% CI 0.174 to 0.356, $P < 0.001$).

Discussion

To the best of our knowledge, this is the first study investigating the mediating effect of sleep disturbance in the association between hypertension and depression. This study highlights that sleep disturbance becomes partial mediation in the association between hypertension and depression. Because the methodology is rigorous and we use a big sample size, hence our study should be considered.

Although the pathological mechanism of sleep disturbance after hypertension was complex. However, it can develop as a result of hypertension due to factors such as persistent physiological stress [28], increased sympathetic nervous system activity causing alertness [29,30], disrupted nighttime blood pressure patterns [31], potential sleep-affecting medication side effects [32], psychological impact from hyper- tension management [33], and endothelial dysfunction [34,35], all of which contribute to sleep disruptions. Effective hypertension treatment, lifestyle changes [36], and stress reduction

Table 2 Lifestyle and comorbid comparison of participants

Variables	Total (n = 19,138)		Missing data		Hypertension (*n* = 2736)		No hypertension (*n* = 16,402)		*p*-value
	n	(%)	n	(%)	n	(%)	n	(%)	
Smoking									< 0.001
Yes	7065	(36.9)			748	(27.3)	6317	(38.5)	
No	12,073	(63.1)			1988	(72.7)	10,085	(61.5)	
Sleep disturbance									< 0.001
Yes	2723	(14.2)			468	(17.1)	2255	(13.7)	
No	16,415	(85.8)			2268	(82.9)	14,147	(86.3)	
Depression									< 0.001
Yes	4068	(21.3)			679	(24.8)	3389	(20.7)	
No	15,070	(78.7)			2057	(75.2)	13,013	(79.3)	
Physical activity during last 7 days									
Vigorous activities									0.68
Yes	4216	(22)			484	(17.7)	3732	(22.8)	
No	14,922	(78)			2252	(82.3)	12,670	(77.2)	
Moderate activities									
Yes	10,908	(57)			1549	(56.6)	9359	(57.1)	
No	8230	(43)			1187	(43.4)	7043	(42.9)	
Low activities									0.001
Yes	13,545	(70.8)			2009	(73.4)	11,536	(70.3)	
No	5593	(29.2)			727	(26.6)	4866	(29.7)	
Did you have outpatient care last 4 weeks?			8	(0.0)					< 0.001
Yes	3716	(19.4)			868	(31.7)	2848	(17.4)	
No	15,414	(80.5)			1868	(68.3)	13,546	(82.6)	
Comorbidity									
Diabetes mellites									< 0.001
Yes	538	(2.8)			233	(8.5)	305	(1.9)	
No	18,600	(97.2)			2503	(91.5)	16,097	(98.1)	
Tuberculosis									0.35
Yes	187	(1)			31	(1.1)	156	(1)	
No	18,951	(99)			2705	(98.9)	16,246	(99)	
Asthma									< 0.001
Yes	513	(2.7)			118	(4.3)	395	(2.4)	
No	18,625	(97.3)			2618	(95.7)	16,007	(97.6)	
Other lung condition									0.48
Yes	332	(1.7)			52	(1.9)	280	(1.7)	
No	18,806	(98.3)			2684	(98.1)	16,122	(98.3)	
Heart attack									< 0.001
Yes	384	(2)			153	(5.6)	231	(1.4)	
No	18,754	(98)			2583	(94.4)	16,171	(98.6)	
Liver disease									0.54
Yes	201	(1.1)			25	(0.9)	176	(1.1)	
No	18,937	(98.9)			2711	(99.1)	16,226	(98.9)	
Stroke									< 0.001
Yes	135	(0.7)			95	(3.5)	40	(0.2)	
No	19,003	(99.3)			2641	(96.5)	16,362	(99.8)	
Cancer									0.01
Yes	140	(0.7)			31	(1.1)	109	(0.7)	
No	18,998	(99.3)			2705	(98.9)	16,293	(99.3)	
High cholesterol									< 0.001
Yes	1031	(5.4)			438	(16)	593	(3.6)	
No	18,107	(94.6)			2298	(84)	15,809	(96.4)	
Kidney disease									< 0.001
Yes	303	(1.6)			83	(3)	220	(1.3)	
No	18,835	(98.4)			2653	(97)	16,182	(98.7	
Stomach or other digestive disease									< 0.001
Yes	2499	(13.1)			503	(18.4)	1996	(12.2)	
No	16,639	(86.9)			2233	(81.6)	14,406	(87.8)	
Psychiatric problem									0.04
Yes	32	(0.2)			9	(0.3)	23	(0.1)	
No	19,106	(99.8)			2727	(99.7)	16,379	(99.9)	

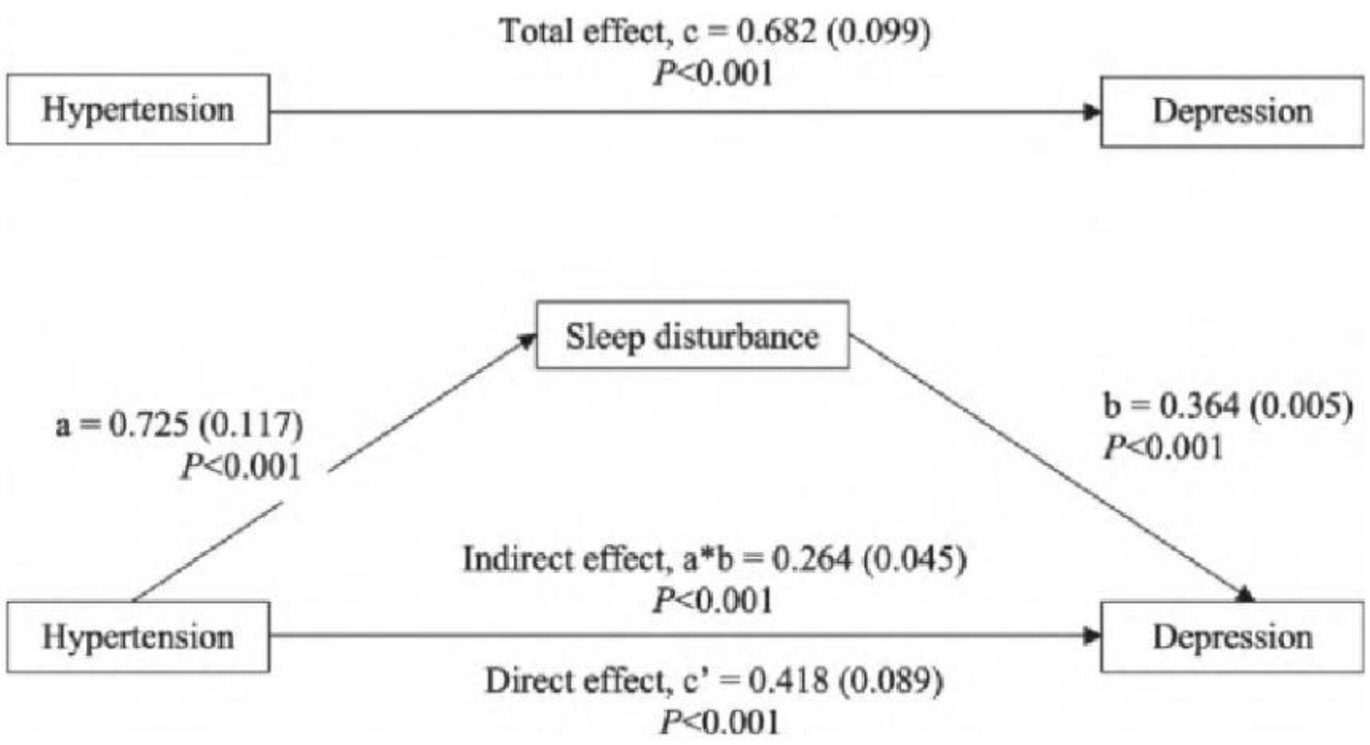
Categorical variables were performed by using chi-square test

Table 3 Associations from multiple linear regression models of hypertension with sleep disturbance, and depression

Predictor	Target variable	Unadjusted			Model 1			Model 2		
		β^a	β^s	(95% Cis)	βa	β^s	(95% Cis)	β^a	β^s	(95% Cis)
Hypertension	Depression	0.68	0.05	(0.49 to 0.88)	0.94	0.07	(0.79 to 1.19)	0.60	0.04	(0.40 to 0.80)
Hypertension	Sleep disturbance	0.73	0.05	(0.49 to 0.96)	0.88	0.05	(0.68 to 1.17)	0.50	0.03	(0.27 to 0.73)
Hypertension	Depression	0.42	0.03	(0.24 to 0.59)	0.66	0.05	(0.47 to 0.84)	0.47	0.03	(0.29 to 0.66)
Sleep disturbance		0.36	0.43	(0.35 to 0.38)	0.37	0.43	(0.35 to 0.37)	0.37	0.44	(0.36 to 0.39)

model 1 = adjusted for variables in Table 1, model 2 = adjusted for variables in Tables 1 and 2
β^a = Unstandardized coefficients, β^s = Standardized coefficients, CI = Confidence intervals

Fig. 2



Mediation Analysis Results. The data were presented in Beta coefficient (standard error)

measures are critical for sleep disturbance [37]. If sleep problems persist, it is critical to consult a healthcare practitioner, as treating hypertension may improve sleep quality [37,38,39].

In this study, sleep disturbance is observed in approximately 17% of the hypertension group and 13.7% of the non-hypertension group. Consistent with previous studies, sleep disturbances such as obstructive sleep apnea (OSA) and insomnia are prevalent following hypertension [32,40,41]. Evidence suggests that OSA becomes a significant risk factor for hypertension [42]. Numerous pathways, including endothelial impairment [43,44], oxidative stress [45,46], inflammation [47,48], and sympathetic activation [49,50], are generally acknowledged as ways in which OSA leads to the development of hypertension. Of note, this study reveals that sleep disturbance partially mediates the association between hypertension and depression. It indicates that targeting depression treatment after hypertension should also consider sleep disturbance.

We found that the prevalence of depression following hypertension in our study is 25% which is higher than in the non-hypertension group (21%, see Table 2). In line with previous studies, the prevalence of depression was ranging from 22 to 32% following hypertension [7,9] and 13–17% in the general population [51,52]. Because the presence of depression affects the health-related quality of life [14]. Hence, it is important for clinicians and researchers to implement the best treatment approach for depression.

Strengths and limitations

To the best of our knowledge, this study possesses several strengths. First, this study was national representativeness of the data since the study population was taken from participants across Indonesia. Second, all interviewers for the IFLS were trained to understand the methodology and the content of the questionnaire.

This study highlights several limitations. First, the data related severity of hypertension, subtype, and type of medication is not available. Second, potential confounders could not obtain such use hypnotic used, dietary factors, and environmental factors, which may threaten the internal validity. Third, the data related to blood pressure and medication for hypertension is unable to be provided. Fourth, the data related to hypertension was self-reported, which may cause information bias.

Conclusion

The result of this study suggested that sleep disturbance plays a role in the etiology of hypertension and depression in adult populations. The management of sleep disturbance could potentially serve as treatment and primary prevention for depression in these populations. Behavioral therapy could be implemented to reduce sleep disturbance.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

IFLS: Indonesian Family Life Survey
CES-D-10: Centers for Epidemiologic Studies Depression Scale
PROMIS: Patient-Reported Outcomes Measurement Information System
IPAQ: International Physical Activity Questionnaire
OSA: Obstructive sleep apnea

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Contributions

FH and KL acquired data, performed the statistical analyses, interpreted data, and drafted and revised the manuscript for important intellectual content and approved the final version. SA, SS, DN, and MS interpreted data, reviewed the analyses, and approved the final version.

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Ethics declarations

Ethics approval and consent to participate
This study was approved by the Institutional review boards at the University of Gajah Mada in Indonesia and the RAND Corporation in the United States with the ethical clearance No. s0064-06-01-CR01.

Consent for publication
Not applicable.

Competing interests

The authors declare no potential conflicts of interest.

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Teenage Blues: Predictors of depression among adolescents in Nigeria

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Lakshit Jain, Editor

Abstract

Background

Depressive disorders, with a prevalence of 15–21%, are among the most common disorders in children and adolescents, and increases the risk of suicide, the second leading cause of death in children aged 10 to 19.

Aim

To determine the prevalence and correlates of depressive disorders among senior students attending secondary schools in Abeokuta.

Method

The study was conducted in five schools randomly selected from a representative sample and was carried out in 2 phases. In the first phase, students were selected via systematic random sampling and given consent forms and GHQ-12 to administer to the parents. In the second phase, students who returned a signed informed consent form and filled out GHQ-12 were interviewed using MINI-KID, Rosenberg's Self-Esteem Scale, Family-APGAR, and sociodemographic questionnaire. Multivariate regression analyses were conducted with p-value <0.05 as level of significance.

Results

The mean age was 15.3 years (SD = 1.27); 48.8% were male. The twelve-month prevalence of major depression was 11.3% and dysthymia was 1.4%. In the final regression analysis, female gender [OR = 4.3, p = 0.046], the experience of bullying [OR = 7.96, p = 0.004], difficulty getting along with friends, [OR = 7.5, p = 0.004], history of sexual abuse [OR = 8.1, p = 0.01], and perceived family dysfunction [OR = 4.9, p = 0,023] were found to be independent predictors of depressive disorders.

Conclusion

Depressive syndromes are a significant health burden in adolescents. Being female, being bullied, having a history of sexual abuse, and family dysfunctionality are risk factors associated with depression among these population.

Introduction

Depressive disorders are among the most common disorders in children and adolescents, with high prevalence of 12% [1] and rising to 21% [1–4]. Depression increases the risk of suicide, the second leading cause of death in children and young adults between ages ten and twenty four [5] and one of the top ten leading causes of death across all ages [5,6]. The reported prevalence of depression among the adolescent population varies widely due to differences in the methodology of various epidemiological studies. Current literature suggests that major depressive disorder is more prevalent than dysthymia and other subtypes of depression [7,8]. Before puberty, there is no significant difference in the prevalence of depression between the genders, but after that, an increased incidence in females is widely documented across various cultures [9,10]. Overall, the prevalence of depression rises with increasing adolescent age [11–13].

Etiological models suggest that exposure to multiple antecedents interacts with innate characteristics

to increase adolescents' risk of depression. Individual risks for depression in adolescents include certain genetic factors, female gender, endocrine dysfunction, negative cognitive styles, sub-clinical depressive symptoms, specific personality traits, and problems in self-regulation/coping behaviors, while risks from the external environment include faulty parent-child relationships, adverse life events and on-going interpersonal difficulties [14–17].

The genetic contribution to the etiology of adolescent depression appears to be moderate, with heritability estimates ranging between 40–70% [14,18]. There is a three to four-fold increased risk of depression in the offspring of adults with unipolar depression compared to children of non-depressed parents [19], which is significantly higher in cases of post-natal maternal depression [20]. This elevated risk is also seen in other forms of parental psycho-pathology, although the association's strength is greatest for parental depression.

Studies have shown that low self-esteem, characterized by global self-devaluation, perceived incompetence, and negative attributional styles, are cognitive factors that markedly increase the risk of depression in adolescents [21,22]. Furthermore, adolescents with a highly emotional temperamental style (neuroticism) characterized by reacting quickly to everyday events, being easily brought to tears, or easily soothed are also recognized to have a significantly elevated risk of depression [23].

Relational conflicts within the family environment play a major role in the etiology of adolescent depression. Studies show that insecure attachment and parenting characterized by coldness, rejection, harsh discipline, and unsupportive behavior are associated with adolescent depressive symptoms [17]. Parental psychopathology, particularly maternal depression, may contribute to chronic interpersonal stress in the family, compromising the quality of parenting, which may negatively affect youths' psychosocial functioning [24]. Other family-based pathogenic factors include physical abuse, neglect, absent monitoring, marital discord, low family cohesion, lack of authoritative parenting, severe acute disruptions such as sudden death or serious illness in a close relative and sudden parental separation [25–27].

Parental depressive symptoms, perception of poor family functioning, peer problems, low self-esteem, female gender, and large family size are some of the factors that have been associated with clinically significant depressive symptoms in adolescents [21]. Other factors that are significantly associated with depression in adolescents include alcohol consumption, drug abuse [28], sexual activity [28,29], and physical violence [28–30]. Lower levels of physical activity has also been linked with severe depressive symptoms [28, 31], while moderate physical activity was linked with reduced risk of depressive symptoms [28].

Depression is markedly increased due to multiple adverse experiences involving longstanding family and more recent friendship events and peer difficulties. Adolescents with poor friendships, characterized by low numbers of friends, infrequent contact, and no intimate relations, are more likely to develop depression, deviant behaviors, and increased social isolation from the desired peer network [22,32,33]. Studies have also shown that adolescents who are bullied and those who are bullies are at an increased risk of depression and suicide [34,35].

Local studies on the prevalence and correlates of depression show findings largely comparable with results from elsewhere. A cross-sectional survey of adolescents in southwest Nigeria found that 5.1% met the criteria for a major depressive disorder (MDD) [4]. A study using the Beck's Depressive Inventory found 9% of school-attending adolescents in another southwestern town in Nigeria to have clinically significant depressive symptoms [21] with a diagnosis of MDD established in 6.9% of the total sample [36]. In another cohort of high school students in a major city in north-eastern Nigeria, a 12% prevalence of depression was reported with 50% of the students who used substances reporting depression [2].

Several studies worldwide have sought to establish the prevalence and associated socioeconomic burden of depressive syndromes in adolescents. However, only a few studies have been done in subsaharan Africa to address the subject [2,7,36–39]. This study aims to determine the prevalence and correlates of depressive disorders among senior students attending secondary schools in Abeokuta.

Materials and methods

The study was carried out in Abeokuta, southwestern Nigeria. It is part of a larger study on anxiety and depressive disorders conducted among secondary school students aged 12–18 years, and the methodology has been described elsewhere [40]. The study was conducted in 2 phases. In the first phase, students were selected via systematic random sampling and given consent forms and GHQ-12 to administer to the parents. In the second phase, students who returned a signed informed consent form and filled out GHQ-12 were interviewed using MINI-KID, Rosenberg's Self-Esteem Scale, Family-APGAR, and sociodemographic questionnaire. Five

schools were randomly selected, and from each school, a proportional sampling method, accounting for the sizes of each school, was employed. The sample size was calculated using the formula for estimating proportions [41].

Study instruments

Sociodemographic questionnaire This was designed to collect data on the sociodemographic characteristics of the participants and factors linked to depression, such as trauma exposure, history of medical illness, etc. It also collected information about family structure and health-related behaviors.

Rosenberg's Self-Esteem Scale The 10-item Rosenberg's Self-Esteem Scale [42] measures both positive and negative thoughts about oneself to evaluate participants' overall sense of self-worth. The responses to each question are given on a 4-point Likert scale, with the options being 'strongly agree' to 'strongly disagree.' Higher ratings on the scale correspond to higher levels of self-esteem. It has been tested on samples of teenage girls from Nigeria [21]. In this study, it was utilized to gauge the degree of adolescent self-esteem.

MINI-KID The Mini International Neuropsychiatric Interview version for children (MINI-KID) is a diagnostic interview specifically developed for children and adolescents aged 6–17 years [43]. It was created to give clinicians a quick, valid, and accurate way to diagnose current DSM-IV and ICD-10 psychiatric illnesses and suicidality in child and adolescent populations. It generally has satisfactory psychometric properties, with excellent reliability estimates: kappa values of 1.00 and 0.72 for inter-rater and test-retest reliability [44]. The MINI-KID was utilized to identify depressive disorders in the study sample. The MINI-KID's current timeframe for the specific depressive disorders was adjusted for this investigation to the previous 12 months. It has been used in studies in Nigeria with good psychometric properties [45,46].

Family APGAR The Family APGAR [47] is a brief screening questionnaire created to get a respondent's opinion of how well their family is doing. It consists of five questions that measure how satisfied respondents are with each of the five aspects of family functioning: adaptability, partnership, growth, affection, and resolve. Each parameter is rated on a 3-point scale: 0 for rarely, 1 for occasionally, and 2 for almost always. A family with a total score of 0 to 3 is likely to be very dysfunctional, 4–6 is likely to be moderately dysfunctional, and 7 to 10 is likely to be highly functioning. In various local investigations, the Family APGAR Score is valid and accurate for evaluating family functioning [48,49]. The participating students finished it without any assistance.

Data analysis

IBM SPSS statistics version 25.0 was used to analyze the study's data. The independent t-test and analysis of variance (ANOVA) for continuous variables and chi-square statistics for categorical variables were used to evaluate the relationships between diagnostic categories and various sociodemographic, family, and psychosocial variables. Post-hoc analysis was conducted on statistically significant variables in the ANOVA analyses, and Fisher's exact test was utilized as needed. Statistically significant variables in the bivariate analyses were entered into a multiple regression analysis model to identify independent predictors of depression. The Kolmogorov-Smirnov test was used to determine whether continuous variables such as age, FAPGAR score, overall academic exam score, and self-esteem score were normal.

Ethical approval

Ethical approval was obtained from the Ethical Committee of the Neuropsychiatric Hospital and the Ogun State Ministry of Education, Science, and Technology, and the administrators of the selected schools granted permission. The parents/guardians of all the participating students also provided written and signed informed consent forms. Additionally, it was made clear to the students that participation was voluntary, and they could decide to withdraw from the study at any time, and not participating would not affect their academic performance. Teachers were not allowed in the room during the interviews to provide extra protection.

Results

A total of 225 students were selected to participate in the study, 5 (1.96%) of them declined to participate (they were all senior secondary school class 3 students; SSS 3 students) who had a significant test the next day, and 6 (2.35%) were excluded because they were older 18 years. The final sample size was 213.

Sociodemographic characteristics

Table 1 summarizes the sociodemographic characteristics. The mean age was 15.3 years (SD = 1.27); 48.8% were male. Only 0.9% of fathers and 1.4% of mothers reported no formal education; and 3.8% of fathers were unemployed compared to 6.1% of mothers.

Child–related psychosocial factors

Table 2 shows child-related psycho-

Table 1: Sociodemographic characteristics of participants.

Characteristic	Frequency (n)	Percentage (%)
Age Group		
12–15	119	55.9
16–18	94	44.1
Gender		
Female	109	51.2
Male	104	48.8
Class		
SS1	54	25.4
SS2	89	41.8
SS3	70	32.9
Religion		
Islam	69	32.4
Christian	144	67.6
Tribe		
Yoruba	189	88.7
Igbo	12	5.6
Hausa/Fulani	3	1.4
Others	9	4.2
Parental Level of Education		
Father		
No formal education	2	0.9
Primary Education	44	20.7
Secondary education	54	25.4
Tertiary education	95	44.6
Unknown	18	8.5
Mother		
No education	3	1.4
Primary education	61	28.6
Secondary education	67	31.5
Tertiary education	71	33.3
Unknown	11	5.2
Parental Employment		
Father		
Not Applicable/unknown	9	4.2
Unemployed	8	3.8
Employed	196	92.0
Mother		
Unemployed	13	6.1
Employed	199	93.4
Not reported	1	0.5

social factors. Sixty-three (29.6%) respondents experienced the loss of a close relative during the previous year; of these, 32 (50.8%) reported a close relationship with the deceased relative. Only 9.9% reported no friends; 13 (6.1%) people admitted to participating in bullying of others; 16.9% reported having experienced bullying; 17 (8.0%) participants had experienced sexual abuse (8.3% of girls vs 7.7% boys); 16 (7.5%) people reported current use of psychoactive substances, with alcohol being the most popular drug (3.3%).

Academic performance

The respondents' converted aggregate English and Mathematics scores ranged between 44 and 72. The median score was 56.0, while the mean score was 57.0 (SD = 6.4). There were no gender differences in academic performances, mean score for males was 57.42(SD = 6.8) compared to 56.61 (SD = 5.9) for females (t = -0.941; p = 0.348).

Rosenberg Self-Esteem Scale

The mean score for the whole sample was 19.07 (SD = 3.5). Boys reported higher scores compared to girls [19.55 (SD = 3.6) vs 18.61 (SD = 3.3; t = -1.997; p = 0.049].

Prevalence of depressive disorders

Twelve-month prevalence for any depressive disorder was 12.2%, major depressive disorder was 11.3% and dysthymia was 1.4%. Twelve-month prevalence for suicidality was 8.9%.

Correlates of depressive disorders

These are shown in Table 3. Female gender (p = 0.049); mother's educational attainment (p = 0.021); perceived family dysfunction ($p < 0.001$); domestic violence ($p = 0.046$); history of sexual abuse ($p < 0.001$), being bullied ($p = 0.001$); experiencing a recent loss ($p = 0.015$); having fewer number of close friends (p = 0.020); and difficulty getting along with friends ($p < 0.001$) were all associated with depressive disorders. There was no association between age, parental psychopathology, sibship, single-parent household, polygamous family setting, use of psychoactive substances and chronic medical conditions, and depression.

Relationship between academic performance and disorder type

The aggregate English and mathematics exam scores were standardized to a normative mean of 50 and a standard deviation of 10. The standardization was done by obtaining a z score, which was multiplied by 10 and added to 50. The standardized scores were then

Table 2

Child-related psychosocial variables.

Psychosocial characteristic		Frequency (n)	Percentage (%)
Recent Loss	No	150	70.4
	Yes	63	29.6
Close Friends	None	21	9.9
	One	35	16.4
	Two	55	25.8
	Three or more	102	47.9
Best Friend	No	46	21.6
	Yes	167	78.4
Friend Interaction	Rarely	9	4.2
	Some days	58	27.2
	Everyday	146	68.5
Getting Along With Friends	Often quarrel/ they don't understand me	23	10.8
	Somewhat well	41	19.2
	Very well	149	70.0
Being Bullied	Rarely/never	177	83.1
	Some days	32	15
	Most days	4	1.9
Bullying Others	Rarely/never	200	93.9
	Some days	13	6.1
Sexually Active	No	204	95.8
	Yes	9	4.2
Sex Frequency	Rarely/never	204	95.8
	Some days	8	3.8
Sexual Abuse	No	196	92
	Yes	17	8
Substance use			
Alcohol Use	Rarely/never	206	96.7
	Some days	6	2.8
	Most days	1	0.5
Cigarette	Use Rarely/never	210	98.6
	Some days	2	0.9
	Most days	1	0.5
Cannabis	Use Rarely/never	207	97.2
	Some days	6	2.8
Chronic Illness	No	182	85.4
	Yes	31	14.6
Involvement in Sport Activity	Rarely/never	108	50.7
	Some days	89	41.8
	Most days	16	7.5

compared between respondents diagnosed with depressive disorders vs. unaffected peers. Respondents with depressive disorder had a mean score of 44.71 (SD = 7.40), which was lower than the mean score of 50.74 (SD = 10.11) for non-depressed peers (t = 2.929; df = 211; $p = 0.004$).

Relationship between self-esteem and disorder type

Participants without depressive disorder had a mean score of 19.67 (SD = 3.181) compared to those with depressive disorder with a mean score of 16.42 (SD = 16.42), ($F = 9.134$, df = 3;209, $p < 0.001$).

Independent predictors of depressive disorders

In the multivariate regression analyses (see Table 4), female gender (OR = 4.250; $p = 0.046$), moderate difficulty getting along with friends (OR = 7.502; $p = 0.004$), the experience of being occasionally bullied (OR = 7.960; $p = 0.004$), history of sexual abuse (OR = 8.055; $p = 0.010$) and moderate family dysfunction (OR = 4.934; p = 0.023) were associated with depression.

Discussion

This study aimed to determine the prevalence and correlates of depressive disorders among senior students attending secondary schools in Abeokuta. The twelve-month prevalence of any depressive disorder was 12.2%, and major depressive episode was 11.3%.

Our study shows that depressive syndromes are a significant health burden in adolescents. The reported prevalence in this study is similar to that reported in other studies [1,2,22]. The apparent convergence of rates is remarkable, given that these studies used different diagnostic instruments. Nevertheless, these findings are higher than elsewhere in Africa [7,36] and the West [50,51]. Differing prevalence periods could explain the varied findings. In addition, the present study used a twelve-month window and found a rate closer to the lifetime rate reported in the US comorbidity survey [1]; lower rates tended to be reported by studies using narrower time frames for prevalence rates.

The prevalence of dysthymia reported in this study was 1.4%, and to the best of the authors' knowledge is the first estimate of the disorder among adolescents in Nigeria. The other available estimate on dysthymia comes from the Nigerian National Survey of Mental Health and Wellbeing (NSMHW) by Gureje et al., which found a twelve-month prevalence of 0.1% in the adult population [52]. Similar prevalence rate of dysthymia has been reported in

Table 3

Correlates of depressive disorders.

		DEPRESSIVE DISORDER				
		No	**Yes**	**χ^2**	**df**	***p*-value**
		n (%)	**n (%)**			
Gender	Female	91 (83.5)	18 (16.5)	3.865	1	**0.049**
	Male	96 (92.3%)	8 (7.7)			
Mother's Education	No formal education	2 (66.7)	1 (33.3)	11.538	4	**0.021**
	Primary	56 (91.8)	5 (8.2)			
	Secondary	64 (95.5)	3 (4.5)			
	Tertiary	56 (78.9)	15 (21.1)			
Domestic Violence	Rarely/never	171 (89.5)	20 (10.5)	6.175	2	**0.046**
	Some days	13 (76.5)	4 (23.5)			
	Most days	3 (60.0)	2 (40.0)			
Family Functioning	Highly Dysfunctional Family	3 (50.0)	3 (50.0)	20.434	2	**0.000**
	Moderately Dysfunctional Family	15 (62.5)	9 (37.5)			
	Highly Functional Family	169 (92.3)	14 (7.7)			
Recent Loss	No	137 (91.3)	13 (8.7)	5.930	1	**0.015**
	Yes	50 (79.4)	13 (20.6)			
Close Friends	None	14 (66.7)	7 (33.3)	9.814	3	**0.020**
	One	31 (88.6)	4 (11.4)			
	Two	50 (90.9)	5 (9.1)			
	Three or more	92 (90.2)	10 (9.8)			
Getting Along with Friends	Often quarrel/they don't understand me	18 (78.3)	5 (21.7)	22.999	2	**0.000**
	Somewhat well	28 (68.3)	13 (31.7)			
	Very well	141 (94.6)	8 (5.4)			
Sexual Abuse	No	177 (90.3)	19 (9.7)	14.468	1	**0.000**
	Yes	10 (58.8)	7 (41.2)			
Being Bullied	Rarely/never	162 (91.5)	15 (8.5)	13.740	2	**0.001**
	Some days	22 (68.8)	10 (31.3)			
	Most days	3 (75.0)	1 (25.0)			

Norway [8] and Uganda [7]. These findings may suggest that although depressive syndromes occur frequently among adolescents, only a small proportion of episodes tend to run prolonged episodes.

In the bivariate analysis, gender and mother's education were the two sociodemographic variables significantly associated with depressive disorders in this study. This significant excess of females among adolescents having a depressive disorder has been replicated in many studies, both local and foreign [31,53]. Gender difference in adolescence generally emerges in middle adolescence, typically by age 13 [53]. This has often led to suggestions that the female excess may be linked to pubertal changes in girls, specifically the achievement of Tanner stage III or IV [53]. However, the changes in body morphology associated with puberty and their resultant psychosocial effects on social interactions and self-perception are insufficient to explain the female adolescent depression excess and underlying changes in androgen and estrogen levels may play a significant mediating role [54].

In this study, depressive disorders appeared to be more prevalent in adolescents with parents with lower educational attainment, although this difference was only significant for mothers' educational attainment. Findings from elsewhere mostly report the reverse to be the case, i.e., adolescents with depression tend to have less educated parents [1,7,22]. While it may be true that for some unknown reasons, depressive disorders occur more frequently in adolescents with better-educated parents in this population, the method of collating the information should be put in perspective. Adolescents' self-report on parental educational attainment might not be a reliable way of determining the parents' highest level of education, so the finding should be interpreted with caution. Parental employment status, as reported by

Table 4

Multivariate logistic regression of independent correlates of depressive disorders.

	B	OR	*p* value	95% C.I. for OR	
				Lower	Upper
Gender					
Female	1.447	4.250	**0.046**	1.026	17.600
Male	Reference	1.00			
Getting Along with Friends					
Quarrelling/misunderstanding	0.114	1.121	0.901	0.186	6.749
Somewhat well	2.183	8.874	**0.004**	2.045	38.514
Very well	Reference	1.00			
Sexual Abuse					
Yes	2.086	8.055	**0.010**	1.965	32.251
No	Reference	1.00			
Being Bullied					
Some days	2.074	7.960	**0.004**	1.965	32.251
Most days	2.317	10.149	0.121	0.541	190.265
Rarely/Never	Reference	1.00			
Family Functioning					
Highly Dysfunctional Family	1.377	3.965	0.301	0.291	54.065
Moderately Dysfunctional Family	1.596	4.934	**0.023**	1.241	19.613
Highly Functional Family	Reference	1.00			

the adolescents, was the other approximate indicator of socio-economic status included in this study, the analysis of which showed that depression was more prevalent in respondents with unemployed parents. However, this difference was not found to be significant. Yet it appears more in keeping with the frequent associations observed between adolescent depression and low socioeconomic status in other studies [55].

The presence of a depressive disorder was significantly associated with the reported occurrence of domestic violence and perceived family dysfunction in this study, similar to findings elsewhere [7,22, 29,36]. Persistent family disagreement through early adolescence increases the general level of low mood and depressive symptoms over time, and it is this rising level of non-clinical negative mood and thoughts that is associated with the onset of later clinical depression in older adolescents [30,56]. Conversely, it may also be true that depressive symptoms in adolescents precipitate conflicts in an otherwise normally functioning family [24,57].

Reported traumatic experiences such as a recent loss within the last year, a history of sexual abuse, and being bullied were seen to be significantly associated with having a depressive disorder in this study, which is similar to other studies [29, 58]. Classic Freudian theory which explains depression as aggression displaced from an external hostile object and turned inwards against the self, provides a psychodynamic framework for understanding this association. However, there is more evidence in the research base to support the cognitive formulation, which proposes that early adverse experiences could result in an enduring triad of negative cognitions about the self, the world, and the future, which then become embedded as a latent negative schema and is activated by subsequent events [59,60]. The significant association between depression and the reported experience of being bullied may be explained by Seligman's learned helplessness theory, which proposes that frequent exposure to uncontrollable and unpredictable events leads to an enduring loss of adaptive behaviors, eventually resulting in permanent deficits in cognitive and emotional processes [61].

Significant associations were also identified with impairments in peer relations in this study. Adolescents diagnosed with depressive disorder tended to report having fewer or no close friends at all and appeared to be experiencing difficulties getting along with friends. This agrees with findings by Field et al., who showed that depressed adolescents had less optimal peer relationships, fewer friends, and were less popular than unaffected peers [62]. Although interpersonal difficulties appear more to be a consequence rather than an antecedent of depression in adolescents, there is evidence that heightened sociotropy (an increased need or desire for peer approval) in the adolescent may render them more vulnerable to depression in the context of ongoing relational dysfunction with friends [62].

Regarding self-esteem, those with depressive disorders reported lower self-esteem compared to those who did not have depression, similar to other studies [21,22,63]. Two possible models explain the observed strong link between depression and reduced self-esteem. The vulnerability model hypothesizes that low self-esteem is a risk factor for depression, whereas the scar model hypothesizes that low self-esteem is an outcome, not a cause, of depression. The direction of causality appears to have been resolved in favor of the vulnerability model by longitudinal studies utilizing cross-lagged regression analyses, which indicated that low

self-esteem predicted subsequent levels of depression and not vice versa [63].

Depressive disorders were significantly associated with reduced academic performance in this study, which is similar to findings by Hysenbegasi and colleagues [64]. Depression is associated with reduced volition, impaired concentration, and a general loss of interest in day-to-day tasks. Beyond potentially causing school absenteeism, affected adolescents might not fully engage in academic activities even when they attend school. Furthermore, intrinsic cognitive deficits are a recognized neuropsychological endophenotype of depression and may further limit academic performance even in the presence of sufficient engagement with school work [65].

In the multivariate regression analysis, female gender, the experience of bullying, difficulty getting along with friends, history of sexual abuse, lower self-esteem, and perceived family dysfunction were found to be independent predictors of depressive disorders, which is similar to what has been reported in other studies from around the world [1,21,22]. Traumatic childhood experiences, in particular, are well-recognized as strong predictors for the subsequent onset of emotional disorders and even other psychiatric disorders [66,67].

The regression model could only explain 50.2% of the variance in depressive illnesses in this study. This shows that a significant percentage of the variation in depressive disorders among adolescents may be explained by factors not considered in the current model, such as biological vulnerability. According to a meta-analysis of the genetic epidemiology of depression, the heritability was around 37% [68]. Such additive genetic factors are thought to moderate the risk of the onset of major depression in part by altering the sensitivity of individuals to some of the depression-inducing psychosocial stressors identified in the present study.

This study comes with some limitations. Firstly, due to the study's cross-sectional nature, causal inferences cannot be made. Secondly, the study was limited to a single city in the Southwest part of the country and may not be generalizable to adolescents in Nigeria. Thirdly, some of the questionnaires were self-reported and may be subject to response bias and social desirability bias, which may affect study validity. Fourth, the small sample size may limit the study's power to detect statistically significant associations. Nevertheless, the final sample size was more than the calculated minimum sample size needed to detect a difference. The study also has strengths: this study went beyond the scope of previous work done in Nigeria on adolescent depression to investigate additional possible correlates, such as parental educational attainment. This study was also the first to report the prevalence of dysthymia among the adolescent population in Nigeria.

In conclusion, this study demonstrated that the prevalence of depressive illnesses in our environment is at par with reports from other parts of Africa and the rest of the world. The study also emphasized characteristics associated with depression, including being bullied, having a history of sexual abuse, having low self-esteem, and family dysfunctionality. Studies with larger adolescent samples that combine structured diagnostic interviews with self-report depression instruments in a two-stage design may be able to find other significant relationships that were missed in the current study. Our study's findings underscore the importance of implementing depression screening initiatives for adolescents in secondary schools in Nigeria. Furthermore, we recommend providing training for guidance counselors to effectively identify and address depression in students exhibiting declining academic performance. Additionally, the prevention of bullying is also an important strategy that should be implemented to curb the incidence of depression among adolescents in secondary schools in Nigeria.

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Data Availability

All relevant data are within the paper and its Supporting information files.

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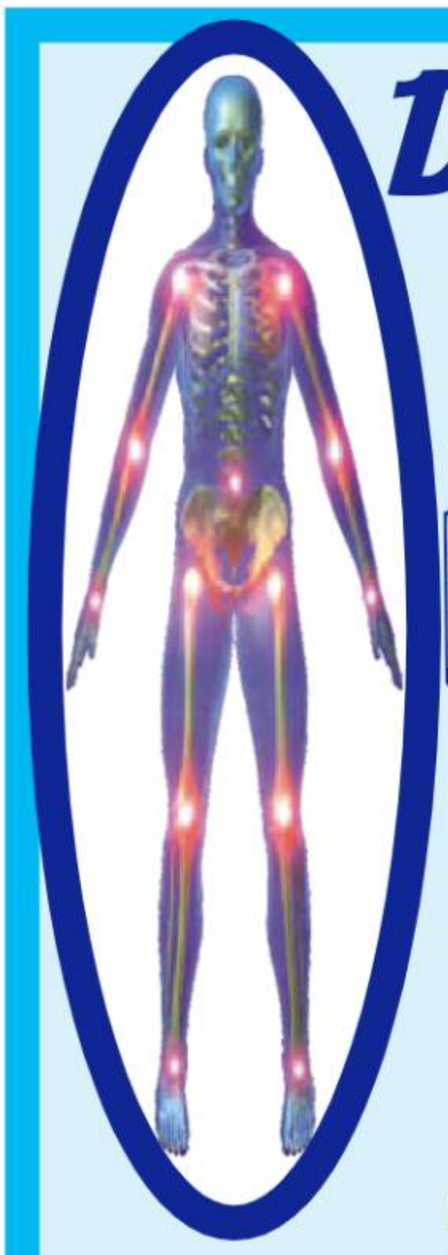

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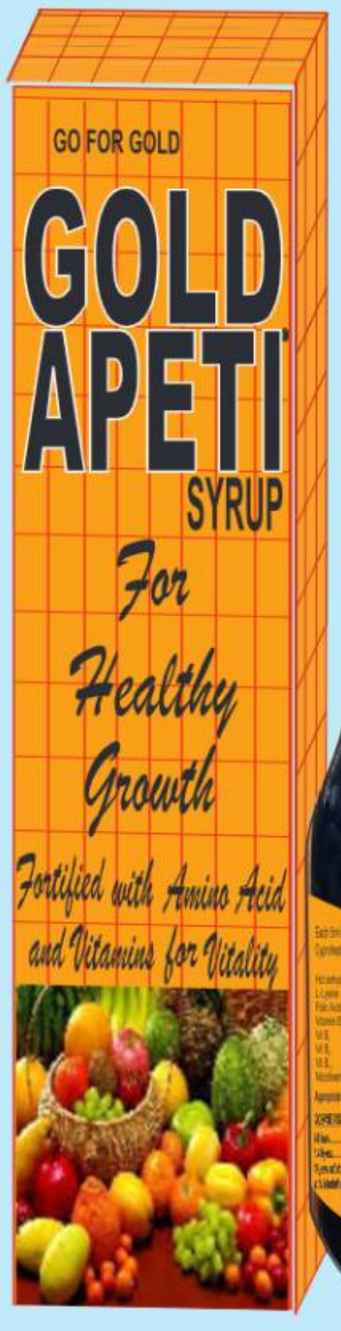

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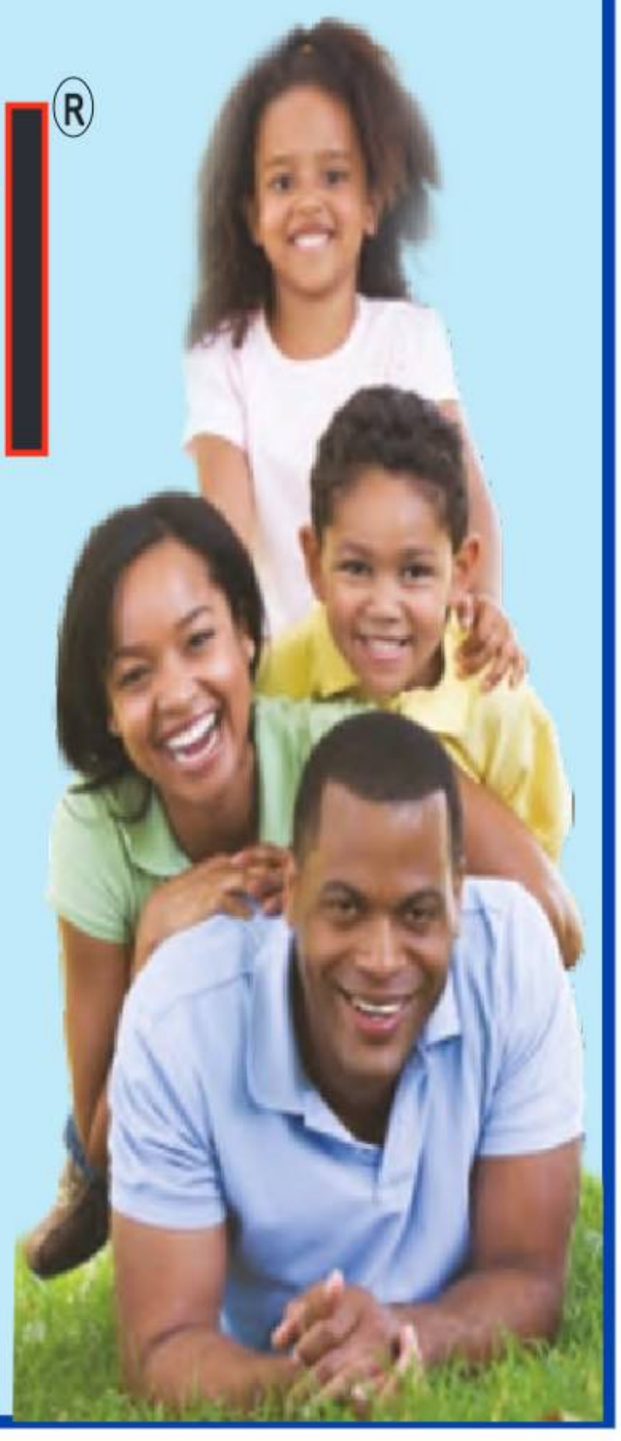

Age-Related Hearing Loss

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A 72-year-old man presents for a routine visit accompanied by his wife. He has no health issues, but his wife volunteers that she has concerns about his hearing. On further questioning, the patient notes problems with hearing and understanding others but attributes these issues to his wife and other family members not speaking clearly. The patient's wife notes that she has heard about the recent availability of over-the-counter hearing aids as well as media reports that hearing loss is linked with the risk of dementia. She wonders whether her husband could benefit from using over-the-counter hearing aids. How would you respond?

The Clinical Problem

Age-related declines in hearing gradually affect every person during life. A person's ability to hear depends on the inner ear (cochlea) precisely encoding sounds into neural signals, which are then processed and decoded into meaning at the cortical level. Pathologic processes that occur at any level of this pathway from the ear to the brain can adversely affect hearing, but age-related hearing loss involving the cochlea is the most common cause.[1]

KEY CLINICAL POINTS

AGE-RELATED HEARING LOSS

- Age-related declines in hearing gradually and progressively affect every person during life, initially manifesting as difficulty understanding speech in background noise or other specific situations.
- Age-related hearing loss detrimentally affects communication and social functioning and is considered to be one of the most clinically significant risk factors for cognitive decline and dementia.
- Management of age-related hearing loss is focused on the use of communication strategies and technologies (hearing aids and cochlear implants) to increase the clarity of the speech signal.
- Evidence from a randomized trial suggests that hearing aid use can improve communication and quality of life and may reduce cognitive loss within 3 years in older adults who are at risk for cognitive decline.
- Technology and regulatory changes now enable adults to self-test and track their hearing using a smartphone (www.hearingnumber.org) and to purchase over-the-counter hearing aids. This approach aligns with broader trends toward empowering consumers with knowledge and options to act on their own health without a clinician intermediary.

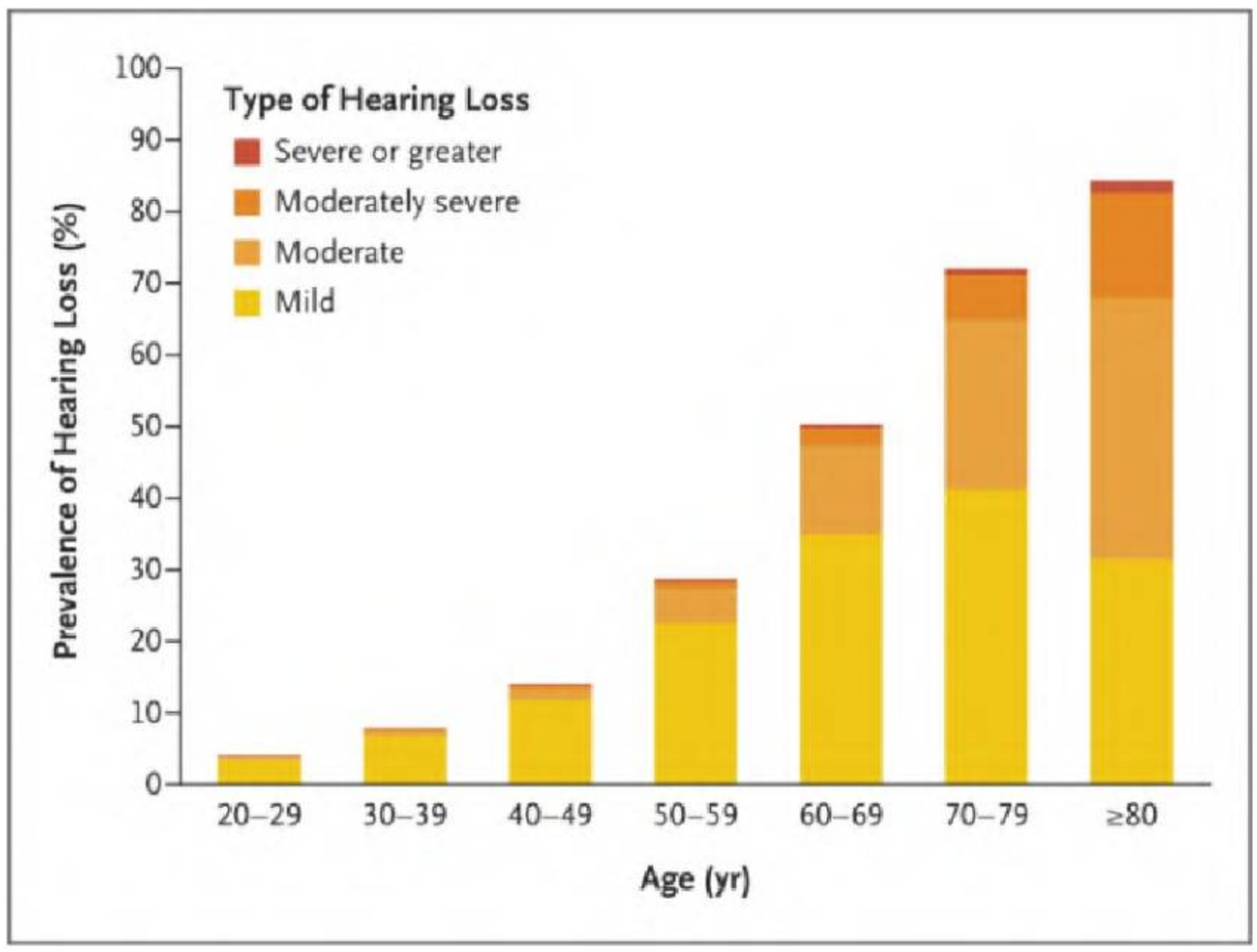
Age-related hearing loss is characterized by the progressive loss of the sensory hair cells of the inner ear, which are responsible for encoding sound into neural signals.[1,2] Unlike other cells throughout the body, sensory hair cells in the inner ear cannot regenerate, and these cells are progressively lost over the course of life owing to the cumulative effects of multiple etiologic processes. The strongest risk factors for age-related hearing loss include older age, lighter skin color as an indicator of cochlear pigmentation (given that melanin is protective in the cochlea), male sex, and noise exposure.[3] Other risk factors include cardiovascular disease risk factors such as diabetes, smoking, and hypertension, which can contribute to microvascular injury to cochlear blood vessels.[3]

Beginning in early adulthood, hearing begins to diminish gradually, particularly with regard to sounds at higher frequencies. The prevalence of clinically significant hearing loss increases across the life span, nearly doubling with every decade of life

such that more than two thirds of all adults 60 years of age or older have some form of clinically significant hearing loss (Figure 1).[3,4] In the United States in 2019, approximately 72.9 million, or one in five, persons were estimated to have hearing loss.[4]

Epidemiologic studies have shown associations between hearing loss and impaired communication, cognitive decline,[5] dementia,[6] higher medical costs,[7] and other adverse health outcomes.[3,8] Research over the past decade has particularly focused on the effects of hearing loss on cognitive decline and dementia, and on the basis of this evidence, the Lancet Commission on Dementia concluded in 2020 that hearing loss in middle and late life was the single largest potentially modifiable risk factor for dementia, accounting for 8% of all dementia cases.[6] The main mechanisms through which hearing loss has been hypothesized to increase the risks of cognitive decline and dementia include adverse effects of hearing loss and impoverished auditory encoding of sound on cognitive load, brain atrophy, and social isolation.[9,10]

FIGURE 1



Prevalence of Hearing Loss in the United States in 2019, According to Age and Severity.

The prevalence and severity of hearing loss increase with age. A person's hearing can be summarized by an average of the hearing thresholds in each ear at the frequencies of sound that are most important for speech (500, 1000, 2000, and 4000 Hz). This summary measure of hearing that is used by the World Health Organization is referred to as the four-frequency pure tone average (PTA4; also called the "hearing number") and indicates in decibels the softest level of speech sound that the person can hear. A PTA4 in the better ear of 20 to 34 dB indicates mild hearing loss, 35 to 49 dB moderate hearing loss, 50 to 64 dB moderately severe hearing loss, and 65 dB or above severe or greater hearing loss. Prevalence data are from the Global Burden of Disease, Institute for Health Metrics and Evaluation, University of Washington (https://vizhub. healthdata.org/gbd-compare/#).

Strategies and Evidence

CLINICAL PRESENTATION

Age-related hearing loss manifests gradually and subtly over time in both ears without any clear inciting event. It affects the audibility and clarity of sounds and a person's everyday communication experience. Persons with mild hearing loss are often not aware of diminishing hearing and instead perceive their hearing difficulties as being attributable to external reasons (e.g., others not speaking clearly and background noise). At greater levels of hearing loss, persons may increasingly notice trouble with speech clarity even in quiet settings and can find conversations in noisier settings exhausting, given the increased cognitive effort that is required for processing the degraded speech signal.[11] Often, family members are most aware of patients' hearing difficulties.

EVALUATION

Evaluation of a patient's hearing issues requires understanding that a person's perception of hearing depends on four components: the quality of the incoming sound (e.g., because the speech signal becomes degraded in rooms with background noise or reverberant acoustics), the mechanical conduction of sound through the middle ear to the cochlea (i.e., conductive hearing), transduction of the acoustic signal into a neuroelectrical signal by the cochlea and transmission to the brain (i.e., sensorineural hearing), and decoding of the neural signal into meaning by the cortex (i.e., central auditory processing) (Table 1). When a patient notes problems with hearing, the cause can lie with any of these components, and in many cases, more than one component is affected before hearing problems become apparent.

The goal of the initial clinical evaluation is to evaluate the patient for readily treatable forms of conductive hearing loss or other forms of hearing loss that may warrant further evaluation with an otolaryngologist. Conductive forms of hearing loss that are readily

TABLE 1 Components Affecting Perception and Understanding of Speech.

Component	Description	Factors That Adversely Affect the Component
Speech signal	Speech is a complex auditory signal composed of sounds of different frequencies, each of different intensity, and all changing in real time and embedded within an auditory soundscape of competing sounds.	Distance from the speech source, reverberant acoustics (generally rooms with higher ceilings and multiple hard surfaces) will distort and degrade speech before it reaches the listener.
Conductive hearing	The pinna, ear canal, tympanic membrane, and middle ear ossicles collect and transduce sound vibrations into pressure waves in the cochlea.	Common processes that can affect conductive hearing include a cerumen impaction that completely obstructs the entire lumen of the ear canal or a middle -ear effusion that can result from eustachian-tube dysfunction caused by an inflammatory process that affects the opening of the eustachian tube (e.g., upper respiratory tract infection and rhinitis). Less common processes include tympanic-membrane perforations or fixation of the middle-ear ossicles
Sensorineural hearing	Sensory hair cells in the cochlea precisely transduce the sonically generated pressure waves into neuroelectrical signals that are transmitted by means of the cochlear nerve to the brain stem and cortex. Injury or damage to cochlear structures results in a degraded and less faithful encoding of speech and other sounds that characterize the auditory soundscape	Age-related hearing loss is characterized by gradual loss of function of the sensory hair cells and other structures of the cochlea, which often result from the combined effects of multiple etiologic factors
Central auditory processing	Decoding of the neural signal from the cochlea into semantic and auditory meaning occurs at the level of the brain stem and higher-order cortical structures	Central auditory processing can be a demanding cortical task in which task difficulty is determined by the quality and fidelity of the ascending neural signal as well as by other factors affecting auditory decoding, such as the availability of visual lip cues from the speaker, semantic context around the speech signal, and the listener's familiarity with the speaker's voice. Impairments with auditory processing and decoding can occur, which are generally related to other conditions that affect brain function (e.g., traumatic brain injury, cognitive impairment, and attention disorders)

treatable by the primary care clinician include otitis media and cerumen impaction and can be apparent on the basis of history (e.g., acute onset with otalgia and aural fullness with an upper respiratory tract infection) or otoscopy (e.g., evidence of complete cerumen impaction in the ear canal). Symptoms and signs accompanying hearing loss that require further evaluation or consultation with an otolaryngologist include ear drainage, abnormal otoscopic examination, unremitting tinnitus, vertigo, fluctuating or asymmetric hearing, or sudden onset of hearing loss without evidence of a conductive cause (e.g., middle-ear effusion).

Sudden sensorineural hearing loss is one of the few forms of hearing loss that requires urgent evaluation with an otolaryngologist (ideally within 3 days after onset) because earlier diagnosis and intervention with glucocorticoids may improve the chances of hearing recovery. Sudden sensorineural hearing loss is a relatively uncommon event, with an annual incidence of 1 in 10,000 persons, and most commonly occurs in adults 40 years of age or older.[12] As compared with a unilateral hearing loss from a conductive cause, patients with sudden sensorineural hearing loss will often report an acute, painless hearing loss in one ear that results in a near-complete inability to hear or understand speech in the affected ear.[12]

Multiple bedside screening methods for hearing loss exist, including whispered-voice and finger-rub tests. However, these measures produce widely varying levels of sensitivity and specificity[13] and may be of limited usefulness depending on the suspected probability of a patient having age-related hearing loss. It is especially important to note that, given the progressive decline in hearing across the life span (Figure 1), some degree of age-related hearing loss can be inferred to be present regardless of screening results on the basis of a patient's age, symptoms indicative of hearing loss, and an absence of other clinical findings suggestive of other causes.

Confirmatory evaluation of hearing loss is performed with referral to an audiologist. During an audiologic evaluation, a patient's hearing is tested with a calibrated audiometer in a sound-attenuating enclosure. The softest intensity of sound in decibels that a patient can reliably detect (i.e., the hearing threshold) is assessed across a range from 125 to 8000 Hz, with lower thresholds being indicative of better hearing. In children and young adults, thresholds across all frequencies will be close to 0 dB, but with progressive age-related declines in hearing, these thresholds will gradually increase, particularly for sounds at higher frequencies. The World Health Organization classifies hearing according to the average of a person's hearing thresholds at the frequencies of sound that are considered to be the most important for speech (500, 1000, 2000, and 4000 Hz), termed the four-frequency pure tone average (PTA4) (Table 2). The PTA4 can be used by the clinician or patient to understand the functional implications of the patient's level of hearing and appropriate management strategies (Figure 2). Other tests that are performed during the audiologic examination (e.g., bone-conduction audiometry and speech understanding) can also help to differentiate whether there may be a conductive or central auditory processing cause of hearing loss and to guide appropriate hearing rehabilitative options.

Evaluations of hearing that patients perform on their own are also increasingly available by means of digital applications. A recently adopted consumer technology industry standard[14] for hearing-related technologies (e.g., smartphones and wireless earbuds) specifies how these applications can directly measure and report to users their PTA4 (also termed the "hearing number"; www.hearingnumber.org), which can be tracked on a regular basis. Such an approach aligns with broader trends toward empowering persons with direct access to metrics to monitor their own health and increases awareness that hearing exists along a continuum that can be monitored and acted on over the course of life, as is done for other health metrics (e.g., blood pressure).

MANAGEMENT

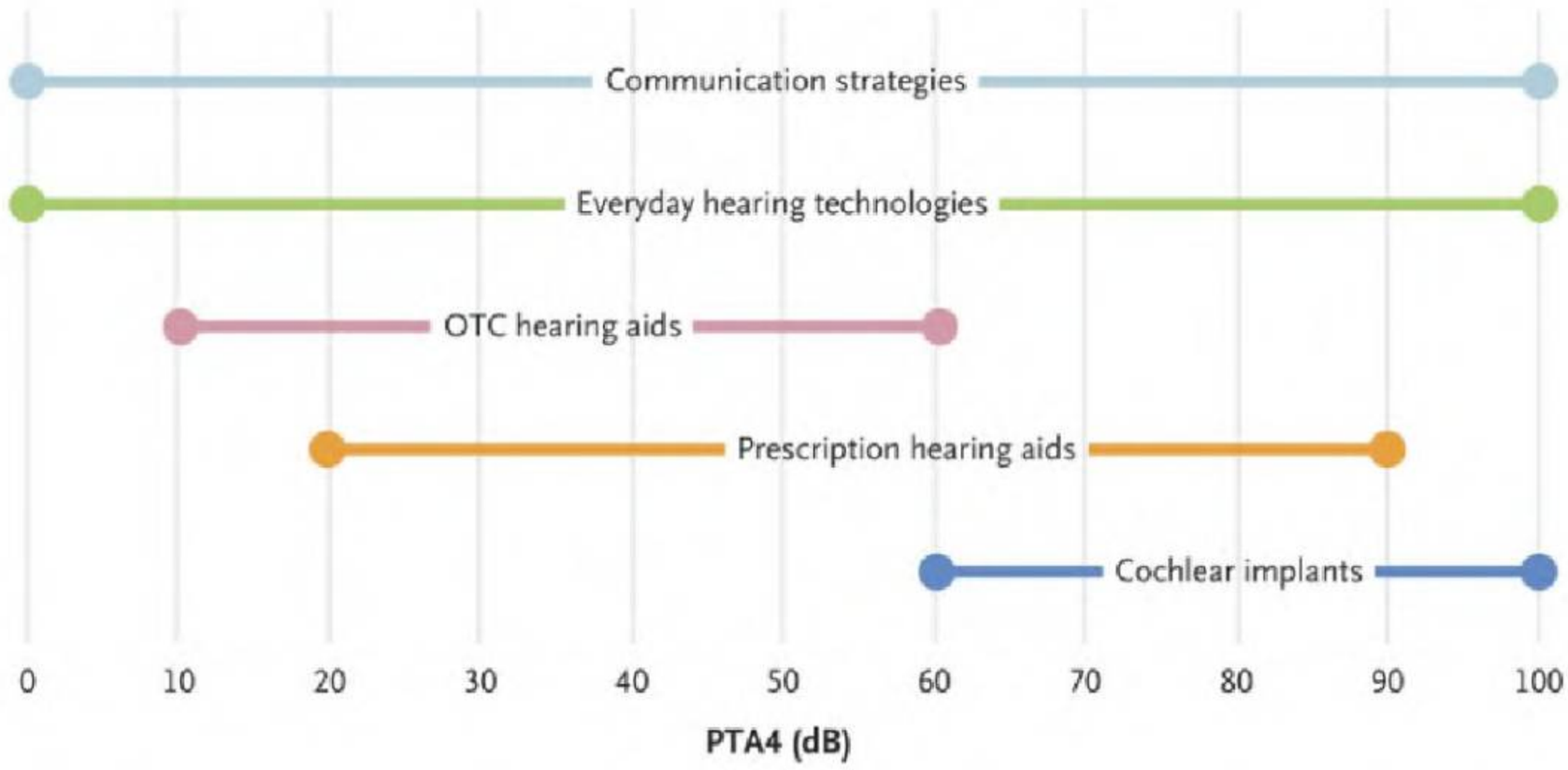
The primary clinical rationale for addressing age-related hearing loss is to enhance a person's access to speech and other sounds in the auditory environment (e.g., music and audible alerts) in order to promote effective communication, engagement with daily activities, and safety. At present, there are no restorative therapies for age-related hearing loss, and management of the condition is focused on hearing protection, adoption of communication strategies to optimize the quality of the incoming auditory signal (over competing background noise), and the use of hearing technologies such as hearing aids and cochlear implants (Figure 2). The prevalence of hearing aid use or cochlear implantation among persons who could benefit (as determined on the basis of their audiologic hearing) remains very low. Among persons with hearing impairment in the United States, the prevalence of hearing aid use is below 20%4 and that of cochlear implantation is less than 5%.[15]

Reasons for the low rate of

FIGURE 2

Management of Age-Related Hearing Loss.

A



B

PTA4 Range	Strategy or Technology	Description
Any level	Communication strategies to improve the clarity or aid in understanding of the speech signal	Get close and face-to-face Being at arm's length from the speaker and being able to see the speaker's face will aid in understanding Avoid rooms with background noise and reverberation Competing sounds distort speech quality Spaces that have soft surfaces (carpets and upholstered furniture) and lower ceilings have less reverberation
Any level	Everyday hearing technologies	Make telephone calls over the Internet when possible Technologies that allow for telephone calls over the Internet, such as Skype, Google Voice, WhatsApp, and FaceTime, have better sound quality than regular landline and cellular telephone calls Use closed captioning Use of captioning or subtitles while watching television or movies makes it easier to understand what is being said
10–60 dB	OTC hearing aids	OTC hearing aids are generally intended for adults with a PTA4 of ≤60 dB The OTC market is just beginning to develop in the United States since federal enactment of regulations on OTC hearing aids in October 2022 OTC hearing aid options are still relatively limited at present with highly variable pricing for a pair of hearing aids ranging from $100 to more than $1,000
20–90 dB	Prescription hearing aids	Prescription hearing aids are for all levels of hearing loss and are obtained with a hearing care provider (generally an audiologist or hearing-instrument specialist) as an intermediary Prescription hearing aids are not covered by traditional Medicare plans but may be covered to some extent by other insurance plans. Prices for a pair of hearing aids range widely from $1,000 to more than $8,000 depending on the wholesale cost of the hearing aids and the costs charged by the hearing care provider for hearing-aid fitting and support services
≥60 dB	Cochlear implants	Cochlear implantation is generally intended for persons with hearing loss of greater severity (PTA4 ≥60 dB in one or both ears) who do not obtain sufficient benefit with a hearing aid for daily communication Cochlear implants are routinely covered by traditional Medicare and most other insurance plans

Panel A shows the general PTA4 ranges at which various strategies and technologies may be useful, and Panel B provides details about the various strategies and technologies that are currently available. OTC denotes over the counter.

TABLE 2

Functional Implications of Hearing on Communication Experience.

PTA4 in the Better-Hearing Ear	WHO Classification of Grade of Hearing Loss	Typical Hearing Experience	
		In QuietIn	Background Noise
<20 dB	Normal hearing	No problem hearing sounds	No or minimal problems
20 to <35 dB	Mild hearing loss	Does not have problems hearing conversational speech	May have difficulty hearing conversational speech
35 to <50 dB	Moderate hearing loss	May have difficulty hearing conversational speech	Difficulty hearing and taking part in conversation
50 to <65 dB	Moderately severe hearing loss	Difficulty hearing conversational speech; can hear raised voices without difficulty	Difficulty hearing most speech and taking part in conversation
65 to <80 dB	Severe hearing loss	Does not hear most conversational speech; may have difficulty hearing and understanding raised voices	Extreme difficulty hearing speech and taking part in conversation
80 to <95 dB	Profound hearing loss	Extreme difficulty hearing raised voices	Conversational speech cannot be heard
≥95 dB	Complete hearing loss	Cannot hear speech and most environmental sounds	Cannot hear speech and most environmental sounds

Adapted from the World Health Organization (WHO) World Report on Hearing (Table 1.3).3 A person's hearing can be summarized by an average of the hearing thresholds in each ear at the frequencies of sound that are most important for speech (500, 1000, 2000, and 4000 Hz). This summary measure of hearing that is used by the WHO is referred to as the four-frequency pure tone average (PTA4; also called the "hearing number") and indicates in decibels the softest level of speech sound that the person can hear. The PTA4 can be used to understand a person's hearing and communication experience in daily life. An audiometric report will typically provide this summary value, or this measure can be obtained by means of a hearing test on a smartphone (www.hearingnumber.org).

adoption are multifactorial and include such factors as stigma, poor accessibility to and affordability of hearing interventions, and the inability of hearing technologies to compensate fully for the degraded peripheral encoding of sound caused by age-related hearing loss.[8]

Hearing-protection strategies are focused on reducing noise exposure by means of movement away from or reduction in the volume of the sound source and by the use of hearing-protection devices (e.g., ear plugs) when needed. Communication strategies include encouraging persons to be face to face and at arm's length when conversing and to reduce background noise. Face-to-face communication allows for both a clearer auditory signal to be received and for the listener to have visual access to facial expressions and lip movements that can aid in central decoding of the speech signal.

Hearing aids remain the primary treatment option for age-related hearing loss. Hearing aids amplify sound, and more advanced hearing aids can also increase the signal-to-noise ratio of the desired target sound (e.g., amplifying a speaker's voice over the background noise) by means of directional microphones and digital signal processing, which is critical for improving communication in noisy settings. Before 2022, hearing aids in the United States could only be purchased with a hearing professional (typically an audiologist or hearing-instrument specialist) as an intermediary.

Beginning on October 17, 2022, the Food and Drug Administration enacted new regulations allowing for the sale of over-the-counter

hearing aids that would be available to consumers, without a hearing professional as an intermediary.[16] These over-the-counter hearing aids are intended for adults with perceived mild-to-moderate levels of hearing loss with PTA4 values generally less than 60 dB, which encompasses 90 to 95% of all persons with hearing loss (Figure 1). In contrast, prescription hearing aids have higher levels of sound output and can be used by adults with more severe levels of hearing loss but are only available with a hearing professional as an intermediary. The cost of these over-the-counter hearing aids once the market is mature is expected to be on par with higher-quality wireless earbuds that often range from $100 to $300 in the United States. Over-the-counter hearing aids may eventually become indistinguishable from wireless earbuds as hearing-aid features become routinely incorpo- rated into these devices.

A previous Cochrane systematic review concluded that hearing aids in adults improve outcomes of both hearing-specific and general health-related quality of life.[17] One recently published randomized trial (Aging and Cognitive Health Evaluation in Elders [ACHIEVE]) investigated the distal effects of hearing intervention (e.g., hearing aids and related audiologic services to support technology use) as compared with health education (control) on reducing 3-year cognitive decline in adults 70 to 84 years of age with hearing loss.[18] In the primary analysis of the total ACHIEVE cohort, hearing intervention did not reduce 3-year cognitive decline as compared with control. However, a prespecified sensitivity analysis showed that in the trial population of participants who were at increased baseline risk for cognitive decline, hearing intervention reduced cognitive change by 48% over a period of 3 years (change in 3-year global cognitive decline, −0.211 SD units in the intervention group vs. −0.402 SD units in the control group). In contrast, no effect of hearing intervention was observed in the trial population consisting of healthy volunteers at decreased baseline risk for cognitive decline. Continued follow-up of the ACHIEVE cohort beyond 3 years and other longer-term studies will be needed to further understand the potential effects of hearing intervention on reducing cognitive decline and the risk of dementia.

Persons who have hearing loss of greater severity (PTA4 values generally ≥60 dB) and who continue to have difficulty with understanding speech despite the use of hearing aids may be candidates for a cochlear implant. A cochlear implant is a neuroprosthetic device that encodes sounds and directly stimulates the cochlear nerve. It is implanted by an otolaryngologist during outpatient surgery that takes approximately 2 hours. A period of 6 to 12 months is needed after implantation for the patient to become accustomed to hearing with the implant and perceiving the neuroelectrical stimuli as meaningful language and sound. Although there is variance in hearing results after a cochlear implant, the improvement in speech under- standing and communication is often described as "life-changing" by many adults who had long struggled to adequately communicate.[19] Potential candidates for a cochlear implant should be referred to a cochlear implant center or an otolaryngologist who specializes in cochlear implantation.

Areas of Uncertainty

Age-related hearing loss results from the combined effects of multiple etiologic factors occurring over one's lifetime.[1,2] Whether pharmacologic or genetic therapies could be feasibly used to reduce the progression of age-related hearing loss or to restore hearing function is an active area of academic and industry research, but efforts have been largely unsuccessful to date.[20] Although several mechanisms have been proposed through which age-related hearing loss could adversely affect health, one provocative mechanism suggests that impaired hearing and diminished auditory afferents may directly affect brain function and structure.[21] Understanding whether existing hearing rehabilitative technologies could modify these effects and help support brain health will be important for optimizing future intervention strategies.

Guidelines

In 2021, the U.S. Preventive Services Task Force determined that there is insufficient evidence to assess the benefits and harms of screening for hearing impairment in asymptomatic adults 50 years or older.[22] Clinicians were advised to use their own clinical judgment about conducting hearing tests in patients who have symptoms of hearing loss or who have raised concerns about their hearing. To my knowledge, no other clinical practice guidelines on age-related hearing loss are currently available.

CONCLUSIONS

The patient described in this vignette presents with a history consistent with age-related hearing loss. After evaluating for and ruling out a potential conductive cause or need for otolaryngology referral, I would presume that some degree of age-related hearing loss is present. I would counsel the patient and his wife about the ways in which age-

related hearing loss as well as other factors can affect perceptions of hearing and how hearing strategies and technologies can improve communicative and social functioning and potentially have distal effects on supporting cognitive health. Depending on the patient's preference, I would refer the patient to an audiologist for a formal diagnostic evaluation and counseling about treatment options or to a well-regarded retail center that sells hearing aids (e.g., Costco). If the patient is familiar with using technology, I would provide resources to help the patient learn how to do a self-test of hearing with a smartphone. I would also discuss the availability of over-the-counter hearing aids and explain that retail choices for over-the-counter hearing aids and support options for these technologies are expected to rapidly increase in the next 2 to 3 years as the market for over-the-counter hearing aids matures in the United States.

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Understanding Sickle cell disease: Causes, symptoms, and treatment options

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Abstract

Sickle cell disease (SCD) is a hereditary blood disorder characterized by the production of abnormal hemoglobin molecules that cause red blood cells to take on a crescent or sickle shape. This condition affects millions of people worldwide, particularly those of African, Mediterranean, Middle Eastern, and South Asian descent. This paper aims to provide an overview of SCD by exploring its causes, symptoms, and available treatment options.

The primary cause of SCD is a mutation in the gene responsible for producing hemoglobin, the protein that carries oxygen in red blood cells. This mutation has abnormal hemoglobin called hemoglobin S, which causes red blood cells to become stiff and sticky, leading to various health complications. Patients with SCD may experience recurrent pain, fatigue, anemia, and increased infection susceptibility.

Treatment options for SCD focus on managing symptoms and preventing complications. This includes pain management with analgesics, hydration, and blood transfusions to improve oxygen delivery. Hydroxyurea, a medication that increases the production of fetal hemoglobin, is commonly used to reduce the frequency and severity of pain crises. Additionally, bone marrow or stem cell transplants can cure select individuals with severe SCD.

Finally, understanding the causes, symptoms, and treatment options for SCD is crucial for healthcare professionals, patients, and their families. It enables early diagnosis, effective symptom management, and improved quality of life for individuals with this chronic condition.

Keywords: acute chest syndrome, disease-modifying therapies, hematopoietic stem cell transplantation, Sickle cell disease, stroke, vaso-occlusive crisis

1. Introduction and background

Sickle cell disease (SCD) is a hereditary blood disorder characterized by the production of abnormal hemoglobin molecules that cause red blood cells to take on a crescent or sickle shape. This condition affects millions of people worldwide, particularly those of African, Mediterranean, Middle Eastern, and South Asian descent.[1] SCD significantly impacts the health and quality of life of individuals affected by the disease. Therefore, understanding the causes, symptoms, and treatment options is essential for healthcare professionals, patients, and their families.

The primary cause of SCD is a mutation in the gene responsible for producing hemoglobin, known as the beta-globin gene (HBB) gene.[2] This gene mutation produces abnormal hemoglobin called hemoglobin S (HbS), which differs from normal adult hemoglobin (HbA) in its molecular structure. HbS causes red blood cells to become stiff and sticky, resulting in

their deformation and reduced ability to flow through small blood vessels.[3] The altered shape of red blood cells contributes to various health complications associated with SCD.

The clinical manifestations of SCD are diverse and can vary in severity among individuals. The hallmark symptom is recurrent episodes of severe pain, known as vaso-occlusive crises, which result from the obstruction of blood flow in small vessels by sickled red blood cells.[4] Fatigue, anemia, and increased susceptibility to infections are also common symptoms of SCD.[5] These manifestations can significantly impact the daily lives of individuals with SCD, affecting their physical and psychosocial well-being.

Treatment options for SCD aim to manage symptoms, prevent complications, and improve the quality of life for patients. Pain management is critical and often involves using analgesics, including opioids, nonsteroidal anti-inflammatory drugs, and adjuvant therapies.[5] Adequate hydration, both orally and intravenously, is essential to maintain proper blood flow and prevent the sickling of red blood cells.[6] In some instances, regular blood transfusions may be required to improve oxygen delivery to tissues and reduce the risk of complications such as stroke.[7]

Hydroxyurea, a medication that increases the production of fetal hemoglobin (HbF), has proven to be effective in reducing the frequency and severity of pain crises in SCD.[8] HbF inhibits red blood cells' sickling, improving their survival and overall clinical outcomes. Furthermore, bone marrow or stem cell transplants can offer a potential cure for select individuals with severe SCD, although this option is limited by donor availability and associated risks.[9]

Understanding the causes, symptoms, and treatment options for SCD is crucial for healthcare professionals to provide accurate diagnosis, effective symptom management, and appropriate counseling for patients and their families. Further research and advancements in gene therapies hold promise for future treatments, offering hope for a better future for SCD patients.

2. Objective of study

This study aims to provide a comprehensive overview of SCD by examining its causes, symptoms, and available treatment options. The study aims to consolidate knowledge on SCD, synthesizing information from reputable sources and scientific literature. By achieving this objective, the study seeks to enhance understanding and awareness of SCD among healthcare professionals, patients, and their families.

Specifically, the study aims to:

Identify the primary cause of SCD, focusing on the genetic mutation in the HBB gene responsible for abnormal hemoglobin production.

Explore the symptoms and clinical manifestations of SCD, including recurrent pain crises, anemia, and increased susceptibility to infections.

Investigate the various treatment options for managing SCD, such as pain management strategies, hydration techniques, blood transfusions, and medications like hydroxyurea.

Assess the effectiveness and limitations of current treatment approaches, highlighting their impact on symptom relief and overall quality of life for individuals with SCD.

Discuss emerging research and potential future treatment options, such as gene therapies and stem cell transplants, which offer hope for improved outcomes and possible cures for SCD.

By addressing these objectives, this study aims to contribute to the knowledge surrounding SCD and provide valuable information for healthcare professionals, patients, and their families. The findings of this study can inform clinical practice, enhance patient care, and promote ongoing research efforts to improve the management and treatment of SCD.

3. Review

3.1. Methodology

This study systematically gathered and analyzed information on SCD causes, symptoms, and treatment options. The methodology involved a comprehensive review of reputable sources, including scientific literature, peer-reviewed journals, and authoritative medical websites. The following steps were undertaken:

3.1.1. Literature search.

A thorough search was conducted using online databases, such as PubMed, Google Scholar, and Medline, to identify relevant articles, reviews, and studies related to SCD. Keywords used in the search included "sickle cell disease," "sickle cell anemia," "causes," "symptoms," and "treatment options."

3.1.2. Inclusion and exclusion criteria.

The search results were screened based on predefined inclusion and exclusion criteria. Only articles written in English and published within the last ten years were considered. Studies on human subjects, clinical trials, and reviews providing comprehensive insights into SCD causes, symptoms, and

treatment options were included.

3.1.3. Data extraction.

Pertinent data and information were extracted from the selected articles. This included details on the genetic basis of SCD, the pathophysiology of the disease, common symptoms and complications, and various treatment modalities. Key findings, statistics, and clinical recommendations were recorded.

3.1.4. Data analysis.

The extracted data were analyzed and organized thematically. Similarities and patterns in the findings were identified, and key concepts related to SCD causes, symptoms, and treatment options were synthesized. Data were then categorized into subtopics for a coherent presentation.

3.1.5. Citation and referencing.

All sources used in the study were adequately cited and referenced. The references were formatted according to the appropriate citation style (e.g., American Psychological Association and Modern Language Association) to ensure accuracy and consistency.

3.1.6. Manuscript composition.

The findings and insights from the analysis were synthesized and used to construct the study abstract, introduction, objectives, and methodology sections.

By employing this methodology, this study ensured a rigorous and systematic approach to gathering and analyzing relevant information on SCD causes, symptoms, and treatment options. The utilization of reputable sources and adherence to inclusion and exclusion criteria enhanced the validity and reliability of the findings.

3.2. Definition and epidemiology

SCD is a globally prevalent hereditary blood disorder with a significant impact on affected individuals and healthcare systems. The epidemiology of SCD varies across different regions and populations. This section provides a detailed overview of the epidemiological characteristics of SCD, including its global distribution, prevalence, and people at risk.

SCD primarily affects populations with ancestral origins in regions where malaria is or has been endemic, including sub-Saharan Africa, the Mediterranean, the Middle East, and parts of India and Southeast Asia.[10] These regions are characterized by a higher prevalence of the sickle cell trait (carrying 1 copy of the mutated gene) due to its protective effect against malaria. Consequently, the incidence of SCD is highest in these areas.

According to estimates, SCD affects millions of individuals worldwide. In sub-Saharan Africa alone, it is estimated that over 70% of all SCD cases occur, with approximately 300,000 affected infants born each year.[11] In the United States, SCD primarily affects individuals of African descent, with an estimated prevalence of 1 in 365 African American births.[12] Other populations with a higher prevalence of SCD include individuals of Hispanic, Mediterranean, Middle Eastern, and South Asian descent.[13]

The prevalence of SCD varies within populations and across geographical regions. In Africa, the prevalence can range from 10% to 40% in certain tribal groups.[14] The prevalence varies among different states in the United States, with higher rates observed in regions with larger African American populations.[15] In some areas of the Mediterranean, such as Saudi Arabia, the prevalence of SCD reaches up to 4%.[16]

The impact of SCD extends beyond prevalence rates, affecting morbidity, mortality, and healthcare utilization. Individuals with SCD face a range of health complications, including acute and chronic pain crises, increased susceptibility to infections, organ damage, and reduced life expectancy.[17] These complications significantly burden healthcare systems, with increased hospitalizations, emergency department visits, and the need for specialized care.

Various factors, including genetic inheritance patterns, geographical location, and socioeconomic factors, influence the epidemiology of SCD. Genetic counseling and carrier screening programs are crucial in identifying individuals at risk of having children with SCD and enabling informed family planning decisions.

Understanding the epidemiology of SCD is essential for public health planning, resource allocation, and the development of effective prevention and management strategies. It helps healthcare professionals and policymakers identify at-risk populations, implement targeted interventions, and improve access to comprehensive care for individuals affected by SCD.

3.3. Pathophysiology

SCD is characterized by a complex pathophysiology involving the abnormal sickling of red blood cells, altered blood rheology, and subsequent tissue damage. The pathophysiological processes in SCD are primarily driven by the structural and functional changes in hemoglobin and the resultant sickle-shaped red blood cells. This section provides a detailed overview of the critical mechanisms underlying the pathophysiology of SCD.

HbS polymerization: The primary abnormality in SCD lies in substituting glutamic acid with valine at the sixth position of the beta-globin chain, leading to the

formation of abnormal hemoglobin known as HbS. Under certain conditions, such as low oxygen tension or dehydration, HbS undergoes polymerization, forming long, stiff polymers within the red blood cells.[3]

Sickling of red blood cells: Polymerization of HbS results in the deformation of red blood cells into a sickle shape. The sickled red blood cells are rigid, less deformable, and prone to hemolysis. These cells cannot flow smoothly through blood vessels, leading to vaso-occlusion and tissue ischemia.[18]

Vaso-occlusion: Sickled red blood cells can adhere to endothelial cells and other sickled cells, forming aggregates that obstruct blood flow in small blood vessels. This vaso-occlusion contributes to tissue ischemia, resulting in acute pain crises, organ damage, and increased susceptibility to infections.[19]

Increased blood viscosity: The presence of sickled red blood cells and increased levels of circulating inflammatory cells and plasma proteins leads to increased blood viscosity in individuals with SCD. This elevated viscosity further contributes to impaired blood flow, vaso-occlusion, and tissue damage.[20]

Oxidative stress and inflammation: SCD is associated with increased oxidative stress due to the presence of free heme and iron released from hemolysis. Oxidative stress triggers inflammatory responses, activation of endothelial cells, and adhesion of sickled red blood cells to the vascular endothelium. This inflammatory cascade further promotes vaso-occlusion and endothelial dysfunction.[21]

Endothelial dysfunction: The interactions between sickled red blood cells and endothelial cells lead to endothelial activation and dysfunction. Endothelial dysfunction produces pro-inflammatory mediators, vasoconstriction, and increased adherence of sickled cells to the endothelium, exacerbating vaso-occlusion and tissue damage.[22]

Ischemia-reperfusion injury: Repeated episodes of vaso-occlusion followed by reperfusion during blood flow restoration can contribute to ischemia-reperfusion injury. This process involves the generation of reactive oxygen species, inflammation, and tissue damage, further exacerbating the pathophysiological consequences of SCD.[23]

Understanding the underlying pathophysiological mechanisms of SCD is crucial for developing targeted therapeutic interventions. Current treatment approaches aim to prevent or mitigate vaso-occlusive crises, manage complications, and improve the overall quality of life for individuals with SCD.

3.4. Causes

SCD is primarily caused by a genetic mutation affecting hemoglobin, the protein responsible for carrying oxygen in red blood cells. The underlying cause of SCD lies in a point mutation in the HBB on chromosome 11, resulting in the production of abnormal hemoglobin known as HbS.[1]

The specific mutation involves a substitution of a single nucleotide, where adenine is replaced by thymine, leading to the substitution of glutamic acid with valine at the sixth position of the beta-globin chain.[2] This alteration affects the structure and function of hemoglobin, causing it to polymerize under certain conditions, such as low oxygen tension or dehydration.

The polymerization of HbS leads to the deformation of red blood cells into a characteristic sickle shape, which is rigid and prone to hemolysis. The sickled red blood cells cannot flow smoothly through blood vessels, leading to vaso-occlusion, tissue ischemia, and subsequent organ damage.[3]

SCD follows an autosomal recessive inheritance pattern, meaning an individual must inherit 2 copies of the mutated gene (one from each parent) to develop the disease. Individuals who inherit 1 copy of the mutated gene and 1 normal gene have the sickle cell trait and are generally asymptomatic but can pass the trait on to their offspring.

The prevalence of SCD is higher in populations with a historical association with malaria, as the sickle cell trait provides some protection against severe forms of malaria infection. As a result, SCD is more commonly found in regions where malaria is or has been endemic, such as sub-Saharan Africa, the Mediterranean, the Middle East, and parts of India and Southeast Asia.[1]

Understanding the genetic basis and underlying cause of SCD has paved the way for advancements in genetic counseling and carrier screening programs. These programs help identify individuals at risk of having children with SCD, enabling informed family planning decisions and providing supportive care for affected individuals and their families.

3.5. Symptoms

SCD is characterized by a wide range of symptoms that can vary in severity and presentation among individuals. The symptoms primarily arise due to the abnormal sickling of red blood cells and subsequent complications. This section provides a detailed overview of the common symptoms associated with SCD.

Pain crises: Recurrent episodes of severe pain, known as vaso-occlusive crises or pain crises, are a hallmark of SCD. These painful episodes occur due to the blockage of blood vessels by sickled red blood cells,

leading to tissue ischemia and inflammation. Pain can occur in various body parts, including the chest, abdomen, bones, and joints.[5]

Anemia: SCD causes chronic hemolytic anemia, characterized by the destruction of red blood cells at an accelerated rate. Anemia can result in fatigue, weakness, paleness, and shortness of breath.[5]

Infections: Individuals with SCD are more susceptible to infections, particularly bacterial infections, due to functional asplenia (loss of spleen) and impaired immune function. Common infections include pneumonia, urinary tract infections, and bacterial sepsis.[24]

Acute chest syndrome: This is a severe complication of SCD characterized by chest pain, fever, cough, and difficulty breathing. It is often caused by infection, pulmonary infarction, or fat embolism and can be life-threatening.[25]

Delayed growth and development: Children with SCD may experience delayed growth and development compared to their peers. Chronic anemia, nutrient deficiencies, and the impact of recurrent pain crises on daily activities can contribute to growth and developmental challenges.[26]

Stroke: SCD increases the risk of stroke, particularly in children. Obstruction of blood vessels in the brain by sickled red blood cells can lead to ischemic stroke. The risk factors for stroke include a history of previous transient ischemic attacks and abnormal blood flow detected by transcranial Doppler ultrasonography.[27]

Organ damage: SCD can lead to long-term organ damage. Organs commonly affected include the spleen (leading to functional asplenia), kidneys (resulting in renal dysfunction), eyes (causing retinopathy), and bones (increasing the risk of avascular necrosis).[5]

It is important to note that the severity and frequency of symptoms can vary among individuals with SCD. Some individuals may experience milder symptoms and better quality of life, while others may have more frequent and severe complications.

Prompt medical attention, comprehensive care, and early intervention are essential in managing the symptoms of SCD and minimizing complications. Regular monitoring, pain management strategies, preventive antibiotics, vaccinations, and supportive care constitute SCD management cornerstone.

3.6. Investigations and diagnosis

The diagnosis of SCD involves a combination of clinical evaluation, laboratory tests, and genetic testing. The aim is to identify the presence of abnormal HbS and assess the extent of the disease. This section provides a detailed overview of the investigations and diagnostic approaches used for SCD.

Complete blood count: A total blood count helps assess the levels of hemoglobin, red blood cells, and other cell types. Due to chronic hemolysis, individuals with SCD typically exhibit a lower hemoglobin level and a higher reticulocyte count.[1]

Hemoglobin electrophoresis: Hemoglobin electrophoresis is a crucial diagnostic test that identifies the presence of abnormal hemoglobin variants. It separates different hemoglobin types based on their electrical charge. It provides information about the relative quantities of HbS and other hemoglobin types, such as hemoglobin A (HbA) and hemoglobin F (HbF).[28]

Sickledex/solubility test: The Sickledex or solubility test is a quick screening test that detects the presence of HbS in a blood sample. It relies on the insolubility of HbS under certain conditions, leading to the formation of sickle-shaped cells. However, this test is less specific than hemoglobin electrophoresis and may require confirmation with additional tests.[18]

Hemoglobin high-performance liquid chromatography: Hemoglobin high-performance liquid chromatography is a more advanced technique for accurately quantifying and identifying different hemoglobin variants. It provides a detailed analysis of the relative proportions of HbS, HbA, HbF, and other hemoglobin types.[29]

Genetic testing: Genetic testing is performed to confirm the diagnosis of SCD and to identify specific mutations in the HBB. This can involve DNA analysis, including polymerase chain reaction, gene sequencing, and other molecular techniques, to detect the presence of the HbS mutation and potentially identify genetic variants.[30]

Newborn screening: Newborn screening programs are implemented in many countries to identify infants with SCD early on. This typically involves testing a blood sample from newborns to detect abnormal hemoglobin patterns. Early diagnosis through newborn screening enables early intervention and comprehensive care for affected infants.[31]

It is important to note that a comprehensive evaluation of individuals suspected of SCD includes a detailed medical history,

physical examination, and assessment of clinical symptoms. Additional tests, such as imaging studies (e.g., ultrasound, magnetic resonance imaging) and specialized evaluations (e.g., transcranial Doppler ultrasound for stroke risk assessment), may be performed to evaluate organ involvement and monitor disease complications.[32]

3.7. Treatment

SCD management aims to alleviate symptoms, prevent complications, and improve the overall quality of life for individuals with the condition. The treatment of SCD involves a multidisciplinary approach that addresses various aspects of the disease. This section provides a detailed overview of the treatment options commonly employed for SCD.

3.7.1. Supportive care.

Pain management: Acute pain crises, a hallmark of SCD, are managed with analgesic medications such as nonsteroidal anti-inflammatory drugs, opioids, and patient-controlled analgesia. Non-pharmacological approaches may also be employed, including heat therapy, relaxation, and distraction techniques.[33]

Hydration: Adequate hydration helps prevent vaso-occlusive crises. Patients are encouraged to drink plenty of fluids, particularly during increased risk, such as infections or exposure to extreme temperatures.

Blood transfusions: Red blood cell transfusions may be administered in specific situations, such as severe anemia, acute chest syndrome (ACA), or stroke. Transfusions help increase the oxygen-carrying capacity of the blood and reduce the percentage of sickled cells.[34]

3.7.2. Disease-modifying therapies.

Hydroxyurea: Hydroxyurea is a medication that stimulates the production of HbF, which inhibits the sickling of red blood cells. It has been shown to reduce the frequency of pain crises, ACA, and hospitalizations. Hydroxyurea is generally well-tolerated, but regular monitoring of blood counts and liver function is required.[8]

Hematopoietic stem cell transplantation (HSCT): HSCT is a potentially curative option for eligible patients, particularly children with severe SCD. It involves replacing the diseased bone marrow with healthy stem cells from a compatible donor. HSCT carries significant risks and requires careful consideration and evaluation of eligibility.[35]

3.7.3. Complication-specific treatments.

Antibiotics: Prophylactic antibiotics, such as penicillin, are often prescribed to children with SCD to prevent infections, particularly those caused by Streptococcus pneumonia. Vaccinations against common bacterial infections, including pneumococcus and meningococcus, are also recommended.[34]

Transfusion therapy: Regular blood transfusions may be indicated in individuals with SCD complications such as stroke or recurrent ACA. Transfusions can help reduce the risk of these complications by decreasing the percentage of sickled cells and increasing the oxygen-carrying capacity of the blood.[34]

Pulmonary hypertension manage ment: In individuals with SCD-related pulmonary hypertension, targeted therapies such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs may be prescribed to improve symptoms and slow disease progression.[36]

3.7.4. Supportive measures.

Comprehensive care: Individuals with SCD benefit from comprehensive care programs that provide regular medical follow-up, psychosocial support, educational resources, and genetic counseling. These programs help individuals and their families manage the disease effectively and improve their quality of life.[29]

Pain crisis prevention: Educating individuals with SCD about pain crisis triggers, hydration, and early recognition of symptoms can help prevent pain crises. Prompt treatment of underlying infections and avoiding exposure to extreme temperatures are essential preventive measures.[37]

It is crucial for individuals with SCD to receive regular medical care from healthcare providers experienced in managing the condition. Treatment plans should be individualized based on the severity of the disease, the presence of complications, and each patient specific needs.

3.8. Complications

SCD has many complications that can affect multiple organ systems. These complications arise due to sickle-shaped red blood cells' abnormal shape and function, leading to vaso-occlusion, tissue ischemia, and chronic hemolysis. This section provides a detailed overview of the common complications seen in SCD.

Vaso-occlusive crisis: Vaso-occlusive crisis is the hallmark complication of SCD and is characterized by the sudden onset of severe pain, often affecting the bones, joints, and

abdomen. Vaso-occlusion occurs when sickled red blood cells block blood vessels, leading to tissue ischemia, organ damage, and intense pain.[24]

Acute chest syndrome (ACS): ACS is a potentially life-threatening complication characterized by fever, chest pain, cough, and shortness of breath. It results from the obstruction of pulmonary blood vessels by sickled red blood cells, leading to lung tissue damage and impaired gas exchange. ACS is a common cause of hospitalization in individuals with SCD.[25]

Stroke can occur in individuals with SCD, particularly children, due to the occlusion of blood vessels supplying the brain. Silent cerebral infarctions are common and can lead to cognitive impairments and neurodevelopmental problems. Transcranial Doppler ultrasound is used to identify children at high risk of stroke.[38]

Chronic anemia: Chronic hemolysis and the destruction of sickled red blood cells result in chronic anemia in individuals with SCD. Anemia can cause fatigue, weakness, and decreased exercise tolerance. Regularly monitoring hemoglobin levels and iron status is essential for managing anemia.[35]

Infections: Individuals with SCD are more susceptible to infections, particularly those caused by encapsulated bacteria such as Streptococcus pneumoniae and Haemophilus influenza. Infections can range from mild to severe, including pneumonia, meningitis, and osteomyelitis. Vaccination against common bacterial pathogens is essential.[39]

Organ damage: SCD can affect various organs, leading to long-term complications:

Renal complications: SCD-associated nephropathy can result in kidney damage and impaired kidney function, leading to chronic kidney disease and renal replacement therapy.[40]

Ocular complications: SCD can cause retinopathy, resulting in visual impairment and blindness. Regular eye examinations are necessary to monitor for retinal changes.[41]

Priapism: Prolonged and painful penile erection, known as priapism, can occur in males with SCD. Priapism requires immediate medical attention to prevent permanent damage to the penis.[42]

Gallbladder disease: SCD increases the risk of gallstones and cholecystitis due to the precipitation of bilirubin in the gallbladder. Surgical removal of the gallbladder may be necessary in severe cases.[43]

Individuals with SCD need comprehensive medical care, including regular monitoring, preventive measures, and early intervention to manage and prevent complications.

4. Conclusion

SCD is a complex genetic disorder affecting millions worldwide. This debilitating condition is characterized by the abnormal shape of red blood cells, leading to a wide range of complications and significant morbidity. Understanding the causes, symptoms, and treatment options for SCD is crucial in improving the quality of life for individuals with the disease.

The causes of SCD are rooted in genetic mutations that result in the production of abnormal hemoglobin. These mutations lead to the formation of sickle-shaped red blood cells that are prone to vaso-occlusion, tissue ischemia, and chronic hemolysis. This process sets the stage for the numerous complications associated with SCD.

The symptoms of SCD can vary in severity and affect multiple organ systems. Vaso-occlusive crises, ACA, stroke, chronic anemia, and infections are some common manifestations of the disease. Prompt recognition and management of these symptoms are essential in preventing further complications and improving outcomes.

Diagnosing SCD involves a combination of laboratory tests, including hemoglobin electrophoresis and genetic testing. Early and accurate diagnosis enables appropriate interventions and the initiation of disease-modifying therapies such as hydroxyurea. Comprehensive care programs that provide regular medical follow-up, psychosocial support, and educational resources are crucial in managing the disease effectively.

Treatment of SCD focuses on supportive care, disease-modifying therapies, and addressing specific complications. Pain management, hydration, blood transfusions, and prophylactic antibiotics are employed to alleviate symptoms and prevent complications. Disease-modifying therapies like hydroxyurea and hematopoietic stem cell transplantation offer potential benefits in reducing the frequency of crises and providing a curative option, respectively.

While significant progress has been made in understanding and managing SCD, much work remains to be done. Further research is needed to advance our knowledge of the pathophysiology, identify novel treatment targets, and improve the overall care of individuals with SCD. By continuing to raise awareness, supporting research efforts, and providing comprehensive care, we can strive to enhance the quality of life for

individuals living with SCD and ultimately work towards finding a cure.

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Abbreviations:

ACA - acute chest syndrome
HbA - hemoglobin A
HBB - beta-globin gene
HbF - fetal hemoglobin
HbS - hemoglobin S
HSCT - hematopoietic stem cell transplantation
SCD - Sickle cell disease

Ethics approval was not required for this review for the following reasons: Nature of the Study: The review is a literature-based analysis not involving primary data collection from human subjects. Instead, it relies on the analysis and synthesis of existing published material.
Confidentiality and Anonymity: As the review does not involve direct contact with human participants, there are no concerns regarding confidentiality, privacy, or the handling of personal data.
Minimal Risk: The review poses minimal or no risk to human participants as it does not involve interventions, experiments, or direct interaction with individuals. The analysis focuses solely on previously published information. Given these factors, the Institutional Review Board (IRB) of Mayo Clinic (IRB ID: 21-007698) has determined that ethics approval is not required for this review. The waiver was granted based on the ethical guidelines and policies outlined by the institution to ensure the protection of human subjects in research.

Author Guarantor: Chukwuka Elendu; elenduchukwuka@ yahoo. com The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Board of the Mayo Clinic (IRB ID: 21-007698).

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Informed consent was not required for this article due to the use of publicly available information and data, which was obtained and analyzed in an aggregated and de-identified manner. The study did not involve any direct interaction or intervention with human subjects, and the research findings were based solely on existing public knowledge and data sources. Therefore, no personal information or individual participation was involved, eliminating the need for informed consent. Patient consent was waived due to the minimal risk nature of the observational chart review study.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]. Commissioned and externally peer reviewed.

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